UNIVERSIDAD COMPLUTENSE DE MADRID
FACULTAD DE MEDICINA

TESIS DOCTORAL

Aplicaciones de la Fisiología Coronaria en escenarios clínicos y angiográficos complejos

Implementation of Coronary Physiology in complex clinical and angiographic scenarios

MEMORIA PARA OPTAR AL GRADO DE DOCTOR

PRESENTADA POR

Enrico Cerrato

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Doctorado en Investigación en Ciencias Médico-Quirúrgicas

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Madrid, 2020

A mia moglie, alla mia famiglia e ai miei amici

TABLE OF CONTENTS

PART III – APPENDIX

PART I

1. RESUMEN

Durante años, la angiografía coronaria constituyó la única herramienta para poder diagnosticar y valorar las consecuencias de la aterosclerosis coronaria, constituyéndose como la referencia estándar en el estudio de la cardiopatía isquémica y dando origen a una terminología que todavía utilizamos de forma rutinaria para describir la severidad de las estenosis coronarias o la gravedad de la enfermedad en base al número de vasos afectados. Posteriormente, la introducción de métodos invasivos para valorar la fisiología coronaria permitió obtener una evaluación precisa respecto a la repercusión fisiológica de las estenosis coronarias epicárdicas, al tiempo que demostró el bajo rendimiento diagnóstico de la angiografía para valorar la repercusión funcional de las estenosis coronarias. Entre las técnicas de fisiología coronaria, la reserva fraccional de flujo coronario (FFR) y el cociente instantáneo libre de ondas (iFR) son las dos más utilizadas en la actualidad y actualmente son recomendadas en la práctica clínica para decidir si la revascularización coronaria esta indicada. Ambas técnicas recibieron el grado máximo de recomendación en las últimas guías europeas de revascularización miocárdica en el contexto de estenosis de grado moderado o de severidad dudosa en pacientes con cardiopatía isquémica estable. Sin embargo, pese a su demostrado valor clínico, la adopción a gran escala de estas técnicas de fisiología es todavía limitado. Se ha señalado que una de las causas que subyacen a la infrautilización de del FFR es que precisa la inducción de estrés farmacológico mediante el uso de fármacos vasodilatadores como la adenosina, que provoca efectos secundarios y conlleva un coste económico añadido, especialmente en un escenario muy frecuente como el de la enfermedad multivaso. Pero sin duda ello obedece también al hecho de que la validación del FFR se realizó fundamentalmente en subgrupos clínicos y anatómicos específicos, como las estenosis de severidad intermedia y la enfermedad coronaria estable. Ello limita la aplicabilidad del FFR y otros índices fisiológicos en otros escenarios muy frecuentes, como los síndromes coronarios agudos o la enfermedad del tronco común izquierdo, o los pacientes diabéticos. Por último, es de reseñar que los índices de presión intracoronaria comparten con la angiografía coronaria una importante limitación: no proporcionar información sobre el estado de la microcirculación coronaria. Este obstáculo impide no sólo el diagnóstico de causas no obstructivas de isquemia miocárdica, sino que también obstaculiza el avance del conocimiento de tratamientos farmacológicos específicos

que puedan aportar un beneficio clínico a través de la modificación de este importante dominio de la circulación coronaria.

El compendio que constituye esta tesis titulada "*Aplicaciones de la Fisiología Coronaria en escenarios clínicos y angiográficos complejos*" está dividido en tres partes. En la primera parte se realiza un breve repaso de la historia y las nociones básicas sobre los índices fisiológicos intravasculares de presión para la evaluación de la cardiopatía isquémica con distintas técnicas de fisiología coronaria. Se realiza también un análisis de los cuadros angiográficos y clínicos complejos en los cuales las aplicaciones de la fisiología presentan todavía limitaciones o están siendo objeto de investigaciones como en la enfermedad del tronco común izquierdo, la enfermedad multivaso y en el síndrome coronario agudo, proporcionando nuevos datos y perspectivas en relación al uso de la fisiología en estos tres marcos. Se introduce finalmente la importancia de la microcirculación en el estudio de la disfunción microvascular.

La segunda parte está compuesta por varios capítulos y contiene tres artículos originales publicados en revistas internacionales. Son estudios originales en los que se utilizan diferentes técnicas metodológicas y estadísticas que van desde un diseño de estudio prospectivo hasta el uso de tecnicas de metaanálisis "study-level", "patient-level" y finalmente en el diseño y desarrollo de un ensayo clínico randomizado, multicéntrico. El objetivo de cada uno de estos trabajos de investigación es intentar proporcionar información novedosa en varios aspectos de la fisiología coronaria en en los tres escenarios clínicos discutidos en la introducción.

El primer estudio, prospectivo y multicéntrico, demuestra que en el contexto de la enfermedad multivaso el uso de técnicas de fisiología combinadas pueden constituir una estrategia válida para incrementar la adopción global de la fisiología intracoronaria cuando otros índices no hiperémicos no están disponibles.

El segundo es un metaanálisis "a nivel de estudio" enfocado en el estudio de una estenosis moderada del tronco común izquierdo basado en el uso del FFR o del ultrasonido intravascular muestra un riesgo de eventos aceptable y similar para ambas técnicas, aunque varias variables diferentes relacionadas con cada técnica demuestran una interacción específica en el resultado.

Finalmente un tercer estudio a través de una técnica de metaanálisis "a nivel de pacientes" analiza la mayor cantidad de datos disponibles actualmente sobre el uso del FFR en el contexto del síndrome coronario agudo y muestra cómo diferir la revascularización con el uso del FFR en arterias no culpables del infarto miocárdico agudo tiene una mayor incidencia de eventos

cardiovasculares mayores cuando se compara con diferir la revascularización en el contexto de la angina estable.

A continuación se presenta el estudio PREDICT, un ensayo clínico randomizado, prospectivo, multicéntrico y original con el objetivo de investigar el efecto protector del fármaco antiplaquetario Ticagrelor en la microcirculación en el marco de la intervención coronaria percutánea en pacientes con diabetes mellitus reportando la publicación del protocolo de estudio y los resultados obtenidos. Es importante destacar que este ensayo clínico fue realizado íntegramente durante el período de doctorado y sus resultados, pendientes de publicación, se reportan por primera vez en esta tesis.

La tercera parte contiene un listado de las publicaciones que componen esta tesis y de otras 130 publicaciones en revistas internacionales no incluidas pero relacionadas con el tema del tratamiento médico o intervencionista de la cardiopatía isquemia y la utilización de técnicas de evaluación de la fisiología coronaria o del imaging intracoronario. La mayoría de estas publicaciones se realizaron durante el periodo del doctorado de manera conjunta con instituciones internacionales involucradas en estos temas de investigación, con las cuales se realizaron proyectos de colaboración estableciendo sinergias de trabajo que van más allá del contenido de esta tesis y que constituyen una posibilidad para continuar el presente tema de investigación en el futuro.

1. ABSTRACT

Cronary angiography was, for many years, the only available tool to diagnose and assess the consequences of coronary atherosclerosis, becoming the standard reference in the study of ischemic heart disease allowing to routinely describe the severity of coronary stenosis or the severity of the disease based on the number of vessels affected. Subsequently, the introduction of invasive methods to assess coronary physiology allowed to obtain a precise assessment regarding the physiological impact of epicardial coronary stenoses, while demonstrating the poor diagnostic performance of angiography to assess the functional impact these stenoses. Among the coronary physiology techniques, the fractional flow reserve (FFR) and the instantaneous wave-free ratio (iFR) are the most used and are currently recommended in clinical practice to decide whether coronary revascularization is indicated. Both techniques received the highest grade of

recommendation in the latest European guidelines for myocardial revascularization in the context of intermediate or doubtful stenosis in patients with stable ischemic heart disease (SIHD). However, despite a growing body of evidence supporting the value of physiology in detecting ischemia, the large-scale adoption of this technique is still limited. It has been pointed out that one of the causes underlying the underuse of FFR is that it requires the induction of pharmacological stress through the use of vasodilator drugs such as adenosine, which potentially causes side effects and an additional cost, especially in a case of need of multiple interrogation in the same coronary tree. Besides, this is certainly due to the fact that the FFR validation was carried out mainly in specific clinical and anatomical subgroups, such as stenoses of intermediate severity and SIHD. The safety of revascularization deferral on the ground of FFR or other physiological indices is also limited in other common clinical settings, such as acute coronary syndromes (ACS), left main coronary artery (LMCA) disease or diabetic patients. Lastly, it should be noted that intracoronary pressure indices share an important limitation with coronary angiography: they do not provide information on the state of the coronary microcirculation. This obstacle not only prevents the diagnosis of non-obstructive causes of myocardial ischemia, but also hinders the advancement of knowledge of specific pharmacological treatments that can provide clinical benefit through the modification of this important domain of the coronary circulation.

The compendium that constitutes this thesis entitled "*Implementation of Coronary Physiology in complex clinical and angiographic scenarios*" is divided into three parts. The first part provides a brief review of the history and basic notions of intravascular physiological pressure indices for the evaluation of SIHD with different techniques. Complex angiographic and clinical scenarios in which the applications of physiology are still limited or under investigation are reported, providing new data and perspectives regarding the use of physiology in challenging settings such LMCA disease, multivessel disease (MVD) and ACS. The importance of microcirculation in the study of microvascular dysfunction is finally introduced.

The second part is composed of several chapters and contains three original articles published in international magazines. Different methodological and statistical techniques are used, ranging from a prospective multicenter study to a study-level and a patient-level meta-analysis up to the design and development of a multicenter randomized clinical trial. Each of these studies aims to provide novel information on various aspects of coronary physiology in the three clinical scenarios discussed in the introduction.

The first prospective, multicenter study shows that in the context of MVD, the use of combined physiology techniques may constitute a valid strategy to increase the global adoption of intracoronary physiology when other non-hyperemic indices are not available.

The second is a "study level" meta-analysis focusing on LMCA intermediate stenosis investigated using either FFR or intravascular ultrasound imaging. An acceptable and similar risk of events was documented for both techniques, while several different clinical and anatomical conditions related to each technique showed an interaction with outcome.

A third study using a “patient-level” meta-analysis technique analyzes the largest amount of data currently available on the use of FFR in the context of ACS showing a significant worse prognosis when a non-culprit lesion in the setting of an ACS is deferred compared with a revascularization deferral of an intermediate stenosis in SIHD.

The randomized, prospective, multicenter and original clinical trial “PREDICT” is also presented in this part reporting the publication of the study protocol and results obtained. This study provides novel insight on the protective effect of the antiplatelet drug Ticagrelor on microcirculation during percutaneous coronary intervention in patients with diabetes mellitus showing that Ticagrelor was associated with a significant decrease in microcirculatory resistance compared to Clopidogrel. Of note, this clinical trial was carried out entirely during the doctoral period and its results are reported for the first time in this thesis.

The third part contains a list of the publications included in this thesis along with 130 other publications in international journals mostly related to medical or interventional treatment of ischemic heart disease using intracoronary physiology or imaging. Most of these publications were made during the doctoral period involving other international institutions committed in these research topics, establishing strong synergies that are beyond the content of this thesis and constitute a potential opportunity to pursue the present line of investigation in the future.

2. ABBREVIATIONS AND ACRONYMS

3VD: Three Vessel Disease
ACS: Acute Coronary Syndrome
ACS-NSTE: Acute Coronary Syndrome with non-ST Segment Elevation
CABG: Coronary Artery By-Pass Grafting
CAD: Coronary Artery Disease
CFR: Coronary Flow Reserve
CVD: Cardiovascular Disease
DES: Drug Eluting Stent
ECG: electrocardiogram
FFR: Fractional Flow Reserve
HR: Hazard Ratio
iFR: instantaneous wave-free ratio
IMR: Index of Microcirculatory Resistance
IQR: InterQuatileRange
IVUS: Intravascular Ultrasound Imaging
LAD: Left Anterior Descending
LCX: Left Coronary Artery
LMCA: Left Main Coronary Artery
MACE: Major Cardiovascular Events
MI: Myocardial Infarction
MVD: Multivessel Disease
MVI: Microvascular Injury
NHPR: non-hyperemic pressure ratios
NSTEMI: non-ST-Elevation Myocardial Infarction
OMT: Optimal Medical Therapy
PCI: Percutaneous Coronary Intervention
PPCI: Primary PCI
RCA: Right Coronary Artery
RCT: Randomized Clinical Trial
SAP: Stable Angina Pectoris
SIHD: Stable Ischemic Heart Disease
STEMI: ST-Elevation Myocardial Infarction
T2DM: Type 2 Diabetes Mellitus
UA: Unstable Angina

Due to their widespread use in scientific literature acronyms in English will be used throughout the thesis.

3. INTRODUCTION

3.1. Limitation of angiography in the decision-making process of coronary revascularization

Selective coronary angiography was pioneered by Sones[1] in 1958. For many years, invasive coronary angiography was considered to be the gold-standard test for the identification of flow-limiting coronary artery disease (CAD). Atherosclerotic coronary artery narrowings, which provoke myocardial ischemia are the most common cause of angina pectoris and lead to adverse cardiac events. Although invasive coronary angiography remains the primary method for identifying coronary artery stenoses, in the past decade, a growing body of evidence have demonstrated pitfalls related of angiographic lesion assessment. This was largely due by the belief that ischemia must be assessed by visual assessment alone based on the severity of the coronary stenosis. However, this two-dimensional angiographic approach roughly simplifies the three-dimensional structure of the coronary vessel as well does not allow to evaluate the degree of ischemia in relationship with the area of subtended myocardium supplied by the target vessel. Several reports have described the discordance between anatomic and functional assessment of coronary lesions, showing that anatomically significant but hemodynamically non-significant lesions or, as opposite, anatomically non-significant but hemodynamically significant lesions were far from be marginal[2] and could consequently lead to a completely wrong treatment of the disease.

3.2 Development of intracoronary physiology indices

The diagnostic capacity of coronary angiography alone was therefore questioned due to its limitations in the comprehensive study of the mechanisms causing myocardial ischemia. Consequently, the research focused on identifying a tool that would allow, in a practical and simple way, to obtain precise information on the true physiological impact of coronary stenosis. After long years of research coupled by technological improvements, two milestone physiology indices were finally developed: the coronary flow reserve index (CFR)[3], and the fractional reserve index (FFR)[4]. The first index is obtained from measurements of coronary flow at rest and during pharmacological stress. CFR integrates information on the state of the epicardial coronary arteries and coronary microcirculation allowing to estimate the overall capacity of the coronary tree to meet myocardial oxygen demands during a stressful situation and could be obtained both

invasively (through a dedicated intracoronary Flow-wire or Doppler-wire) or non-invasively[5], using conventional echocardiography[6], myocardial contrast perfusion echocardiography[7] or Positron Emission Tomography (PET) scanning[8]. Several studies were performed demonstrating the ability of Doppler wire-derived CFR to identify physiologically important coronary narrowings and to guide percutaneous coronary intervention (PCI)[9]. These experiences, however, highlighted some important limitations of this technique, which hindered its implementation in everyday clinical practice including (i) technical aspects of obtaining an acceptable Doppler signal (ii) the lack of an absolute normal value of CFR (iii) alterations of resting flow conditions (i.e. changes in heart rate, blood pressure, left ventricular contractility) which may affect the reproducibility of CFR[10]. Finally, as mentioned before, CFR interrogates the status of the entire coronary circulation, both the epicardial vessel and the microcirculation limiting the use of CFR for separating ischemia-producing epicardial disease from concomitant microvascular dysfunction.

Differently, FFR is obtained from invasive measurements of coronary pressure, using intracoronary guides specifically developed for this purpose. Its determination requires vasodilation of the microcirculatory tree through the use of hyperemic drugs such as adenosine. The FFR makes it possible to specifically and accurately assess how an epicardial stenosis affects myocardial perfusion in the corresponding coronary territory, and indirectly represents the percentage of the maximum coronary blood flow obtained through a coronary stenosis, with respect to the maximum flow that would be expected to be found in the absence of such stenosis[4]. In clinical practice, the measurement of intracoronary pressure parameters is simpler than the measurement of coronary flow parameters and more reproducible than a measurement obtained in a resting condition. For all the aforementioned reasons, the FFR demonstrated to be more feasible and reproducible, compared to CFR[11], and was consequently increasingly incorporated into clinical practice.

In the last decade physiological assessment of CAD has become one of the cornerstones of decision making for myocardial revascularization. Beside the FFR, other pressure-based indexes for functional assessment of coronary stenoses were developed and largely tested in clinical trials. Furthermore, physiology allows to explore microvascular status in patients without obstructive CAD. In the next paragraphs different intravascular modalities to assess both the epicardial vessels and the microcirculation were briefly described along with current evidence supporting their use in clinical practice.

3.3 Clinical relevance of intracoronary pressure physiological indices

3.3.1 Intracoronary stenosis evaluation with a hyperemic pressure index: Fractional Flow Reverse (FFR)

The importance of measuring translesional pressure gradients to gain further insight into the hemodynamic consequences of an epicardial stenosis has also been recognized for many years. Grüntzig et al[12] assessed the adequacy of the first percutaneous transluminal coronary angioplasty by measuring the residual resting pressure gradient across the treated lesion (**Figure 1**).

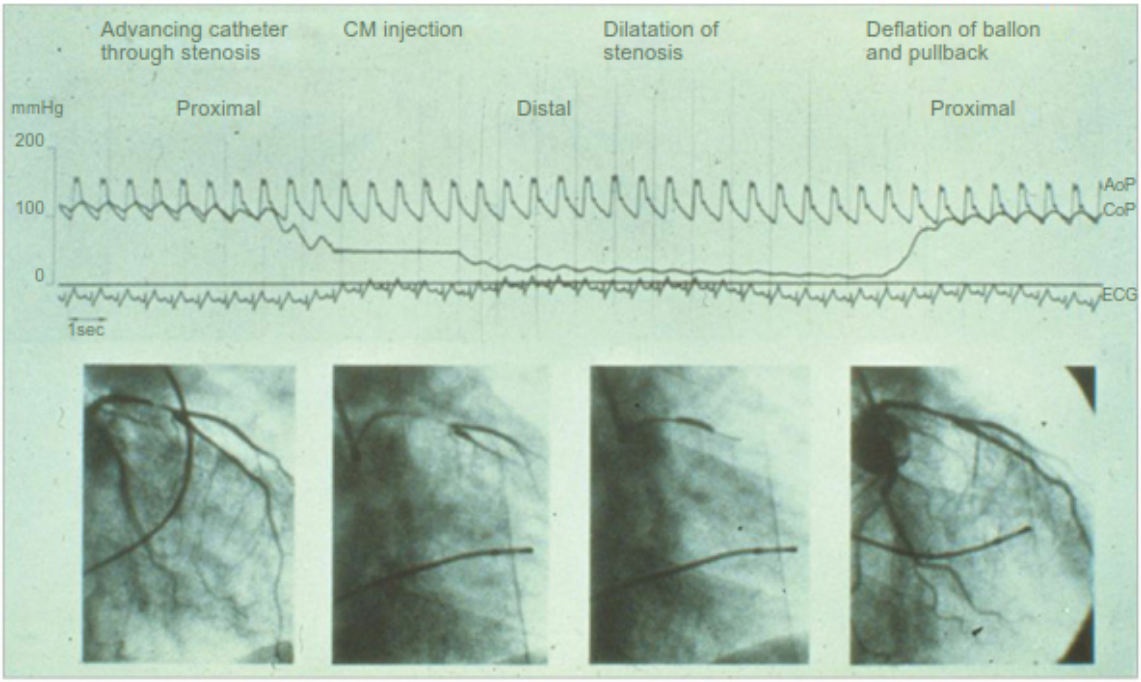

Figure 1. First case of percutaneous coronary intervention. In 1979, coronary pressure across the stenosis before and after balloon angioplasty was recorded in the first case of coronary intervention. AoP, aortic pressure; CM, contrast media; CoP, coronary pressure. Reproduced with permission from (Grüntzig. et al, N Engl J Med 1979; 301:61-68.), Copyright Massachusetts Medical

These initial efforts were hampered by the overestimation of pressure gradients because of the size of the end-hole catheters used to measure distal pressure and by the lack of use of hyperemic agents. Despite early introduction to the field of PCI, practical use of coronary physiology in the catheterization laboratory did not begin until the late 1990s because of

technological and theoretical aspects. After the introduction of the concept of hyperemia, the relationship between coronary pressure and coronary flow was actively investigated. FFR was first described by Pijls et al. in 1993[4]. The concept of FFR is based on the fact that maximal hyperemia could achieve a near correlation between coronary flow and coronary pressure because coronary resistance is stable and minimal during maximal arterial dilation. Consequently, FFR is defined as the ratio of mean distal pressure (Pd) relative to mean aortic pressure (Pa) during maximal hyperemia induced by vasodilating agents. Taking into account stenosis severity, myocardial territory and viability, and collateral perfusion, FFR is able to assess the functional significance of CAD. The cutoff value to detect significant ischemia was suggested to be 0.75 by a relatively small study, which demonstrated high diagnostic performance of FFR, with a sensitivity of 88%, specificity of 100% and accuracy of 93% compared with dobutamine stress echocardiography, stress myocardial perfusion scintigraphy and exercise stress electrocardiography[13]). Nowadays, the best cut-off value to defer PCI in clinical practice is 0.80 after validation in multiple prospective, randomized trials (**Table 1** and **Figure 2**).

Three major randomized trials was fundamental in establishing evidence of FFR: the DEFER[14], the FAME[15] and the FAME2[16] trials.

a. DEFER (Deferral Versus Performance of PTCA in patients without documented ischemia) study: was conducted to evaluate the safety of deferring PCI guided by FFR. In that study, patients with stable angina pectoris (SAP) and intermediate stenosis but FFR >0.75 were randomized to deferral (deferral group) or revascularization (perform group). Subsequent to this original report, long and longer-term follow-up of the DEFER cohort is now available at 5 years[17] and 15 years[18]. Event-free survival did not differ between the deferral and perform groups. According to this findings, in patients presenting with SAP with FFR >0.75 stenting did not decrease the risk of cardiac events for CAD.

b. FAME (Fractional Flow Reserve Versus Angiography for Multivessel Evaluation) study: the second RCT study was performed to assess the effectiveness of FFR-guided PCI compared with angio-guided PCI in patients with multivessel CAD. In this trial, 1005 patients with at least 50% stenoses of the vessel diameter in at least 2 of the 3 major epicardial coronary arteries were randomly assigned to undergo PCI with drug-eluting stents (DES) guided by FFR measurements or guided by angiography alone. The cutoff value for decision-making was 0.80.

The result indicates that FFR-guided PCI significantly reduced the rate of MACE (death, nonfatal myocardial infarction, and repeat revascularization) at 1 year (13.2% vs 18.3%; 95% CI, 0.54 - 0.96, p = 0.02). Consequently, the cutoff value of 0.80 became the threshold to define stenoses generating significant ischemia.

c. FAME 2 (Fractional Flow reserve-Guided PCI versus Medical Therapy in Stable Coronary Disease) Study: The third trial was the FAME 2 study to examine whether FFR-guided PCI plus optimal medical therapy (OMT) was superior to OMT alone or not. This RCT was designed to enroll 1220 patients with 2-year clinical follow-up. However, due to an unexpected higher occurrence of urgent revascularization in OMT alone group the study was halted with a mean follow-up of 7 months. In summary, FFR-guided PCI plus OMT, as compared with OMT decrease the need of urgent revascularization. No definite conclusions were drawn regarding the hard endpoint of death or myocardial infarction.

Trial	Study Design	N	Follow-up	Design	Primary endpoint	Main findings	FFR cut-off used
DEFER	Multicenter, RCT	325	15 yrs	PCI with Bare Metal Stents vs FFR-guided deferral	Event-free survival at 2 years follow-up	PCI when FFR ≥0.75 do not give advantage in terms of survival	<0.75
FAME	Multicenter, RCT	1005	5 yrs	Angio-guided vs. FFR-guided PCI with DES	MACE (Death, non-fatal MI or repeat revascularization) at 1 year	FFR-guided PCI in multivessel CAD reduce	≤0.80
FAME 2	Multicenter, RCT	888	1 yr		MACE (Death, non-fatal MI or urgent revascularization) at 2 year	Significant reduction in urgent revascularization in FFR-guided PCI + OMT arm, with trend towards significance in death/MI (the trial was stop prematurely)	≤0.80

Table 1: Pivotal RCTs in Fractional Flow Reserve and clinical outcome. DEFER: Deferral Versus Performance of PTCA in patients without documented ischemia; FAME: Fractional Flow Reserve Versus Angiography for Multivessel Evaluation; FAME 2 (Fractional Flow reserve-Guided PCI versus Medical Therapy in Stable Coronary Disease).

Despite this growing body of evidence supporting the value of FFR in detecting ischemia, the implementation of FFR was marginal in clinical practice. Potential causes for this include the following:

1. prolongation of procedural time especially in case of multivessel coronary disease requiring multiple interrogation with repeated boluses of adenosine or prolonged intravenous infusion of adenosine;
2. additional cost for pressure wire and adenosine or other drugs;
3. discomfort or side effect during vasodilator drugs administration in a non-negligible percentage of cases;
4. failure to achieve maximal hyperemia in specific subset of patients with chronic impairment of microcirculation like obese or diabetics
5. paucity of data regarding the safety of deferral in specific subset such in the context of an Acute Coronary Syndrome

Consequently, to simplify and expand the use of functional evaluation of coronary stenosis in the real world, especially for those who, for financial, logistic or other reasons, cannot (or do not want to) use adenosine, alternative hyperemic agent like medium contrast injection (contrast-FFR: cFFR) was proposed. Several authors[19–21] advocate cFFR as a simple way of inducing a somewhat lower degree of hyperaemia that could be enough for disclosing "significant" lesions in an important proportion of cases, thus circumventing the use of adenosine. cFFR resulted to be reliable in PCI-deferral or treatment when its value was respectively > 0.87 and < 0.84 while a "grey-zone" was defined when cFFR falls between 0.84 and 0.87. Studies comparing the diagnostic performance with adenosine-derived fractional flow reserve (FFR) concluded that cFFR offers a universal technique to simplify invasive coronary physiological assessments. Yet FFR remains the reference standard for diagnostic certainty as even cFFR reached only ~85% agreement[20].

Following this concept, a novel hybrid strategy was tested in an original study included in the present thesis and will be discussed above (**Part II, 2.1.2**).

3.3.2 Introduction of non-hyperemics pressure ratios (NHPRs) indices: instantaneous wave-free ratio (iFR) and other indices

In 2012 the instantaneous wave-free ratio (iFR) was introduced. iFR measures the ratio of distal coronary to aortic pressure during a period in diastole where microvascular resistance is naturally stable. By only measuring pressure within this specific portion of the cardiac cycle, iFR facilitates the pressure-only assessment of the haemodynamic impact of a coronary stenosis without the need of hyperemic agents[22,23]. The wave-free period was calculated beginning 25% of the way into diastole (identified from the dicrotic notch of pressure waveform) and ending 5 ms before the end of diastole. The iFR concept has been initially tested in direct comparison with FFR[22,23]. Thereafter, two large randomized trials[24,25] in coronary physiology ((2042 patients in iFR SWEDEHEART [Evaluation of iFR vs FFR in Stable Angina or Acute Coronary Syndrome], 2492 patients in DEFINE-FLAIR [Functional Lesion Assessment of Intermediate Stenosis to Guide Revascularisation]) randomised patients with coronary stenosis of intermediate severity to undergo either FFR-guided or iFR-guided revascularisation, using cut-off values for FFR and iFR of 0.8 and 0.89, respectively. Both trials included stable angina patients and also those with ACS with non-culprit intermediate disease. These 2 RCT reached the same conclusion: iFR-guided PCI was noninferior to FFR-guided PCI in the selection of the vessels to be treated or deferred and in the resulting rates of MACE at 12 months (**Table 2** and **Figure 2**).

Trial	Study Design	n	Follow-up	Design	Primary endpoint	Main findings	FFR/iFR cut-off used
DEFINE-FLAIR	Multicenter, RCT, double blinded	2492	2 yrs	iFR-Guided vs FFR-guided PCI	MACE: Death, non-fatal MI or unplanned revascularitazion at 1 year follow-up	Non-inferiority of iFR compared with FFR with respect to MACE at 1 year	FFR≤0.80 iFR≤0.89
iFR SWEDEHEART	Multicenter, RCT, open label	2037	2 yrs	iFR-Guided vs FFR-guided PCI	MACE: Death, non-fatal MI or unplanned revascularitazion at 1 year follow-up	Non-inferiority of iFR compared with FFR with respect to MACE at 1 year	FFR≤0.80 iFR≤0.89

Table 2: Pivotal RCT in instantaneous wave-free ratio and clinical outcome. iFR SWEDEHEART: Evaluation of iFR vs FFR in Stable Angina or Acute Coronary Syndrome; DEFINE-FLAIR: Functional Lesion Assessment of Intermediate Stenosis to Guide Revascularization

Following these findings, European Society of cardiology (ESC) guidelines[26] were revised and gave a Class I (Level of Evidence: A) recommendation for guiding PCI in both iFR and FFR

Since the validation of iFR, other Non-Hyperemics Pressure Ratios (NHPRs) have been developed. Actually the ones commercially available are the following three (**Figure 2**):

- diastolic hyperemia-free ratio (Boston Scientific, Marlborough, Massachusetts);
- diastolic pressure ratio (Opsens Medical, Quebec, Quebec, Canada);
- resting full-cycle ratio (RFR) (Abbott, Abbott Park, Illinois).

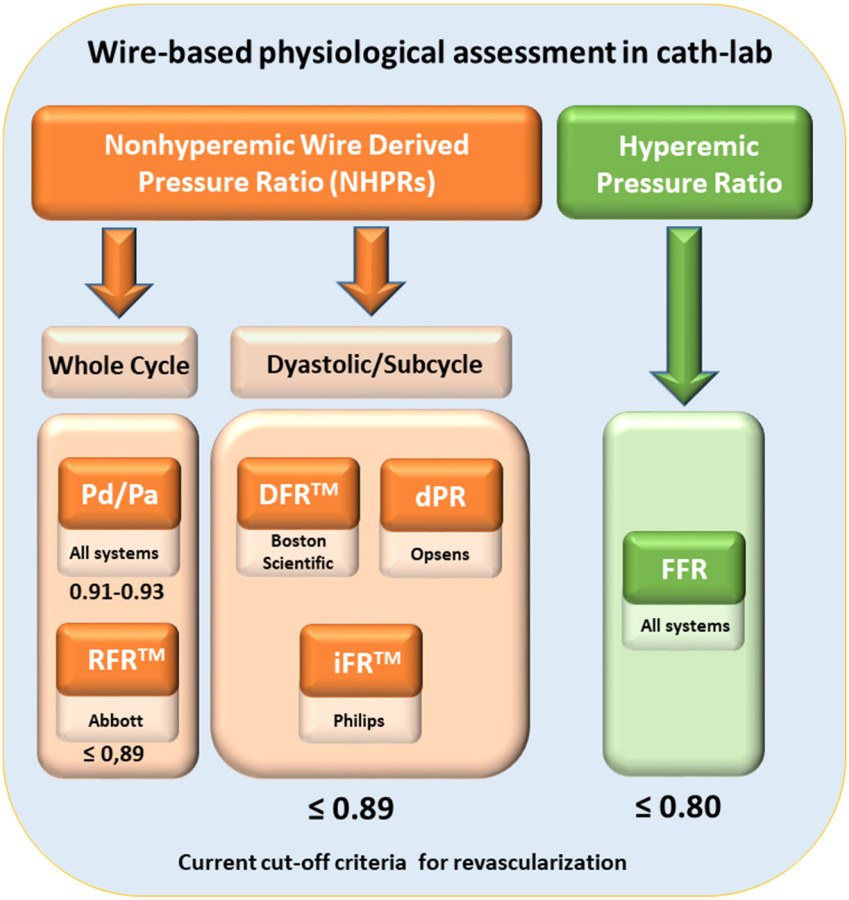

Figure 2. Hyperemic and non-hyperemic wire-based pressure ratios indices

All these three required a dedicated console and wire to be performed. Differently, the ratio of distal coronary pressure (Pd) to aortic pressure (Pa) is the oldest NHPRs and it is available with all pressure wire. It was validated with FFR and iFR in limited clinical settings even showing an excellent agreement with iFR[27]. Conversely its use is limited by a lower signal-to-noise radio contributing to higher influence of pressure drift on measurements[28].

All these 6 NHPRs are identical to iFR both numerically and with respect to their agreement with FFR[29] and demonstrate in retrospective studies an excellent agreement with iFR[30,31](**Figure 3,4**). However, differently from FFR and iFR, no RCTs have evaluated the impact of NHPR-guided PCI on clinical outcomes. There is a great likelihood that they will be non-inferior to FFR or iFR-guided PCI and may ultimately result in a wider adoption of physiological assessment in everyday practice.

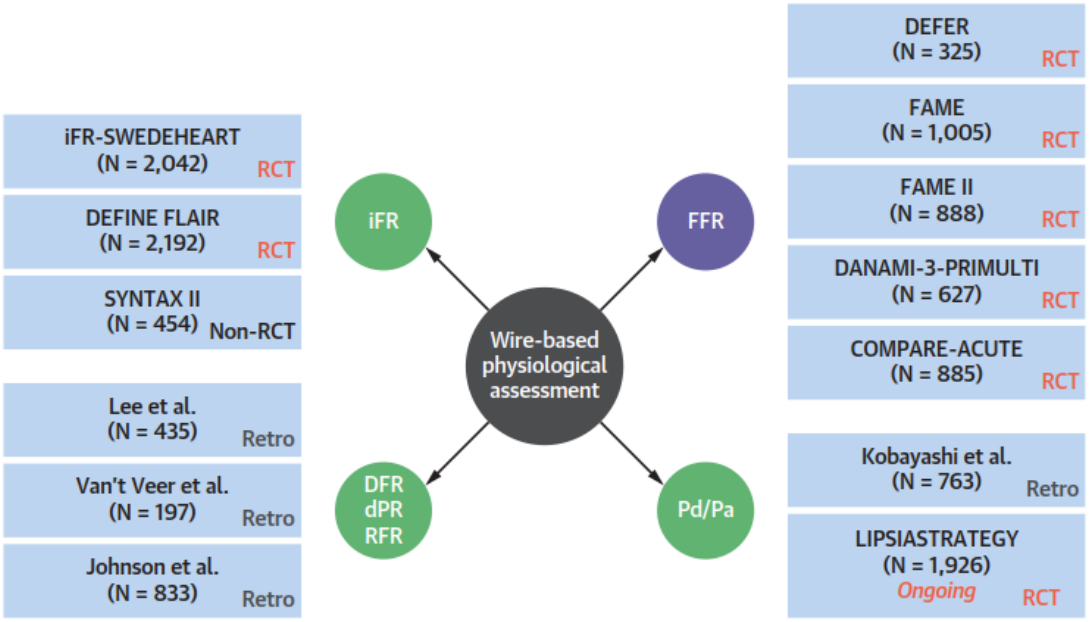

Figure 3. Wire-based physiological assessment with major trials respectively; DANAMI-3-PRIMULTI = Danish Study of Optimal Acute Treatment of Patients With ST-Elevation Myocardial Infarction–Primary PCI in Patients With ST-Elevation Myocardial Infarction and Multivessel Disease: Treatment of Culprit Lesion Only or Complete Revascularization;; DEFINE FLAIR = Functional Lesion Assessment of Intermediate Stenosis to Guide Revascularisation; DFR = diastolic hyperemia-free ratio dPR = diastolic pressure ratio; FAME = Fractional Flow Reserve Versus Angiography for Multivessel Evaluation; iFR = instantaneous wave-free ratio;iFR-SWEDEHEART = Evaluation of iFR vs FFR in Stable Angina or Acute Coronary Syndrome; LIPSIASTRATEGY = Comparison of Pd/Pa Versus FFR in Intermediate Coronary Stenoses; RCT = randomized controlled trial; Retro = retrospective; RFR = resting full-cycle ratio; SYNTAX = Synergy Between PCI With Taxus and Cardiac Surgery. Reproduction with permission from Kogame, N. et al. J Am Coll Cardiol Intv. 2020;13(14):1617 – 38

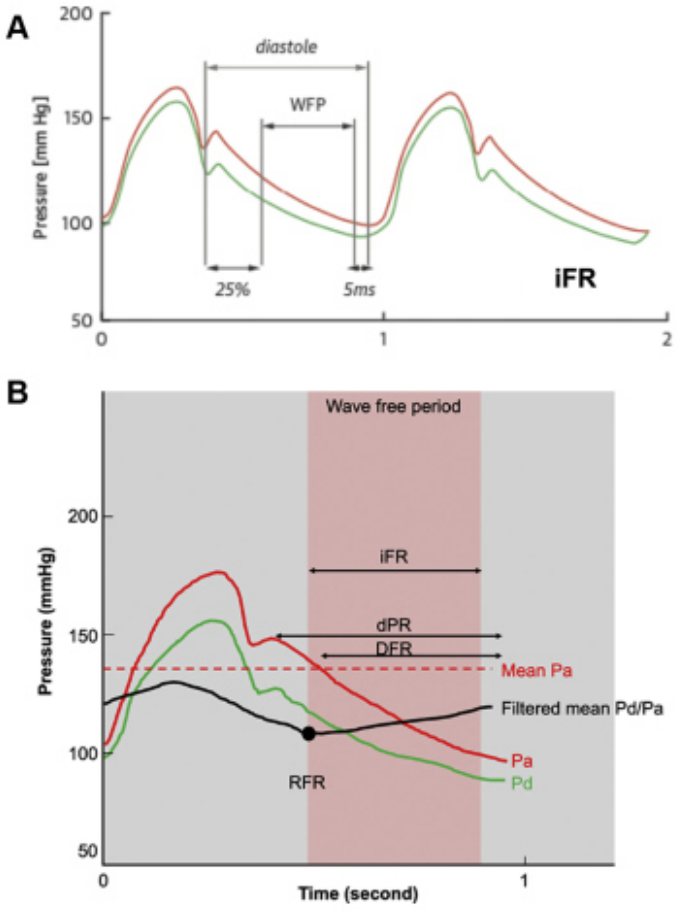

Figure 4. Instantaneous wave-free ratio (iFR) is defined as average Pd/Pa during the wave-free period (WFP) (pink shaded area). The WFP was calculated beginning 25% of the way into diastole and ending 5 ms before the end of diastole (A). Diastolic pressure ratio (dPR) is defined as average Pd/Pa during entire diastole (B). Diastolic hyperemia-free ratio (DFR) is defined as average Pd/Pa during Pa less than mean Pa with negative slope (B). Resting full-cycle ratio (RFR) is defined as the lowest filtered mean Pd/Pa during the entire cardiac cycle (B). Reproduction with permission from Kogame, N. et al. J Am Coll Cardiol Intv. 2020;13(14):1617 – 38

3.3.3 Evaluation of Microvascular disease with pressure and flow assessment

Hyperemic and (NHPRs) indices are a valuable tool to assess obstructive causes of IHD, but it does not inform about the concomitant presence of a non-obstructive involvement generally secondary to microcirculatory dysfunction. Differently from the large capacitance vessel of the epicardium, the microcirculation is controlled through an interplay of metabolic, myogenic, endothelial and neural factors all of which may be involved in its dysfunction[32,33]. Intravascular physiology allows the exploration of the microvascular domain in heart disease and has the

potential to obtain information with prognostic relevance. Therefore, a growing interest in invasive coronary physiology along with new technological developments, allows to assess intracoronary pressure and flow in the cath-lab. At present, there are several methods that allow such intravascular quantification of the microvasculature, perhaps each with specific advantages and drawbacks. In the next paragraphs two intravascular modalities to assess the microcirculatory status, the Coronary Flow Reserve (CFR) and the Index of Microcirculatory Resistance (IMR) will be described along with the prognostic information provided. The practical aspect of calculations of these indices is reported in **Figure 5**.

3.3.3.1 Coronary Flow Reserve

Since coronary flow and resistance are inversely related, microvascular function can be measured by integrating pressure and temperature measured simultaneously using thermodilution-based measurements of coronary artery flow and pressure. These measurements named CFR can be made using a pressure- and temperature-sensitive coronary guidewire[34]. CFR represents the vasodilator capacity of the coronary vascular bed during hyperaemia and is measured by indicator thermodilution. A bolus of saline (i.e. 3 mL) at room temperature injected through the guide catheter will mix with antegrade coronary blood flow at body temperature, causing a transient reduction in temperature that is measured by the thermistor, located 3 cm from the distal end of the guidewire. The thermodilution curve is reflected by a transit time. Accepting the variability that may occur with this type of measurement, the mean transit time for three saline injections is displayed at rest and during pharmacological hyperaemia.

CFR, the ratio of resting-to-hyperaemic blood flow, was the one of first intravascular investigative tools implemented for assessing the coronary circulation[3].

A precise cut-off to define an abnormal CFR is not well established. This is partly due to the nature of microcirculation that, unlike a coronary stenosis, cannot be defined diseased according to a single cut-off.

One of the advantage of CFR is that it could be performed also non-invasively using conventional echocardiography[6], myocardial contrast perfusion echocardiography[7] or Positron Emission Tomography (PET) scanning[8]. This fact allowed to expand the methodology to a larger population than would be possible solely with invasive techniques.

CFR has been incorporated in several studies proven particularly insightful in many different subset of research, both in SAP and in ACS setting.

In SAP setting, PET-derived CFR has been shown to be abnormal in multiple conditions such hypertension[35], dyslipidemia[36], smoking[37], left ventricular hypertrophy[38], aortic stenosis[39].In stable patients with T2DM a low CFR was detected as a marker of early microcirculatory impairment[40]

CFR showed to be related with a cardiovascular events occurrence and mortality at long term both using transthoracic echocardiography[41] or PET-derived CFR[42]. Notably, in presence of intermediate coronary stenosis, CFR demonstrated to be a more powerful predictor of long-term occurrence of major adverse cardiac event than an abnormal FFR[43].

In ACS, after successful revascularization of an acute myocardial infarction, a reduced CFR is associated with the presence of microvascular obstruction on MRI[44]. Moreover, CFR after primary PCI can predict the likelihood of ventricular recovery and in hospital mortality[45]

However, despite the availability of CFR to interrogate the myocardium a number of caveats exist in its use. Coronary thermodilution measurements require brisk saline injections during resting and hyperemic conditions to calculate CFR based on the average mean transit time of three saline boluses. Although it is considered correlate well to absolute coronary flow in research settings[46] this method is prone to measurement errors due to the sensitivity to the saline injections, and due to the fact that the rapid saline injections may disturb coronary hemodynamics. Moreover, many other factors (age, female sex, volume expansion, increase heart rate…) may influence resting coronary flow producing a relative changing in CFR[47]

3.3.3.2 Index of Microcirculatory Resistance (IMR)

The IMR allows the clinical assessment of microcirculatory resistance. It is relatively simple to obtain using a dedicated wire and console. It is growingly used as tool to appraise microcirculatory function in the catheterization laboratory[48]. IMR could be calculated as the product of the distal pressure measurement (Pd) with hyperemic thermodilution-derived time (Hyperemic T_{mn}, **Figure 5)**. This index provide a reliable measurement of microvascular function independently from hemodynamic perturbation and has been tested and validated in animals and

humans[10,49]. Differently from CFR, IMR provides and independent assessment of the microvasculature being ultimately more informative in this setting.

IMR has been used in different scenarios:

a. ACS setting: after primary PCI, IMR was found to correlate with myocardium viability on PET scans and to left ventricular recovery as estimated by 6-month echocardiography[50]. Subsequent studies provided similar results in STEMI patients using MRI-derived microvascular obstruction or MRI-myocardial salvage as parameters of comparisons[51,52]. After acute phase of acute MI, IMR (along with Hyperemic T_{mn} and CFR) showed a gradual improvement in the following 6-months[44]. Regarding long-term outcome, an absolute IMR value > 40 was reported[53] as an independent predictor of death or re-hospitalization for heart failure up to 3 years of follow-up in the largest study on IMR after acute MI (hazard ratio 2.1; P=0.034). Finally IMR was recently reported to be an independent predictor of long-term survival in ACS patients undergoing PCI in two RCT trials on this topic[54–56].
b. SAP setting: IMR was able to predict the risk of periprocedural MI[57] and also to demonstrate a potential advantages of direct stenting in reducing the distal embolization as compared to lesion predilation with a balloon[58].

Interestingly, IMR was used to test adjuvant therapies in order to appraise their potential beneficial effect on microvascular injury. In elective PCI, intracoronary administration of angiotensin-converting enzyme inhibitors[59] or pre-treatment with statins[60] resulted in an improvement of IMR values post-PCI implying that a proper preventive "preparation" of microcirculatory beds could be beneficial in reducing the damage related to distal embolization of particles potentially released from vulnerable plaques the PCI target lesion. At the time of primary PCI, repeated intracoronary administration of Nicorandil (a nitric oxide donor) showed a reduction in IMR with a positive effect during myocardial infarction[61].

Recently several authors report on different antiplatelet agents regiment on microvascular function as assessed by IMR, mainly in the setting of ACS[54–56]. This topic will be covered elsewhere (**Part II**) along with the discussion on the original study focusing on this topic and included in this thesis

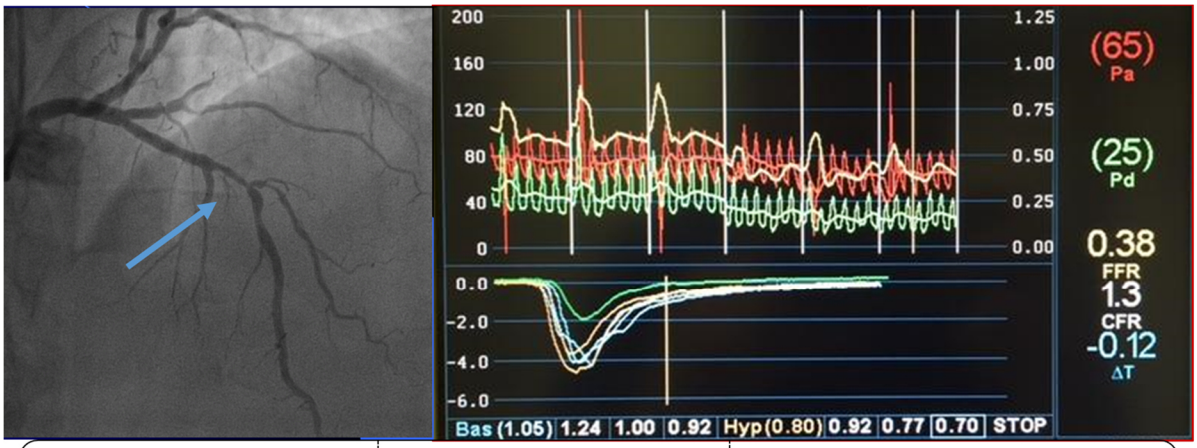

Figure 5. Calculation of Fractional Flow Reserve, index of microvascular resistance and coronary flow reserve in an angiographic tight stenosis involving mid Left Anterior Descending. IMR, index of microvascular resistance; Pd, distal pressure; Tmn, mean transit time; CFR, coronary flow reserve; FFR, fractional flow reserve.
An intracoronary pressure and temperature sensor-tipped guidewire (St. Jude Medical) will be used to measure distal coronary pressure and to derive thermodilution curves as previously described (24). Three thermodilution curves will be obtained from a hand-held, 3-ml rapid (<0.25s) injection of room temperature saline at baseline and during maximal hyperemia, which will be achieved by infusion of 140 µg/kg per minute of adenosine via the femoral vein.
Mean transit time (Tmn) at baseline and during maximal hyperemia will be derived from the thermodilution curves. Simultaneous recordings of mean aortic pressure (guiding catheter, Pa) and mean distal coronary pressure (distal pressure sensor, Pd) also will be obtained at baseline and during maximal hyperemia. The CFR will be calculated from the ratio of hyperemic to baseline Tmn. The IMR will be calculated using the following equation: IMR = PaxTmn[(Pd-Pw)/(Pa-Pw)], where Pw is the coronary wedge pressure. Pw will be measured as the distal

3.4 Clinical and angiographic scenarios in which the evidence for the use of coronary physiology is currently limited

As mentioned above, there are specific subset of coronary stenosis or clinical conditions in which patients might benefit from FFR interrogation but there is still limited evidence to support its use or FFR use may be hindered by technical issues preventing an optimal hyperemic status or need of additional time or costs. Among these scenarios, the present thesis sough to provide novel data on the followings ones:

- Multivessel coronary disease (MVD)
- Left main coronary artery disease (LMCA)
- Acute coronary syndrome (ACS)
- Diabetic type 2 patients (T2DM)

3.4.1 Multivessel Coronary Disease

After the introduction of newer-generation DES, PCI is currently widely performed MVD. However, long-term clinical outcomes of PCI in 3-vessel disease (3VD) is less satisfactory than expected despite newer DES use when revascularization is guided by angiography alone[62]. On the matter of fact, FAME trial[63] explore the benefit of FFR-guided PCI in MVD in stable patient. The 2-year rates of mortality or myocardial infarction were 12.9% in the angiography-guided group and 8.4% in the FFR-guided group (p=0.02). Additionally, number of stents used per patient was significantly lower in the FFR-guided group (1.9 ±1.3 vs 2.7 ±1.2; p <.001)[64].

Similarly, in a study[65] from South Korea group encompassing more than five thousand patients, the rates of MACE at 1 year was significantly lower in patients after the routine FFR use vs. patients before the routine use of FFR (hazard ratio 0.55; 95% confidence interval 0.43-0.70; P < 0.001). This was primarily due to a reduction in peri-procedural MI and repeat revascularization. Taking together, current evidence indicate that the decision made with angiography in multivessel stable disease lead to worse outcome in comparison with a physiology guided strategy leading to a reclassification of the treatment strategy up to 40% of patients with CAD. Therefore, angiographic 3VD might be reclassified as 1- or 2-vessel CAD, which could benefit from PCI and not require Coronary Artery By-Pass Grafting (CABG, **Figure 6**).

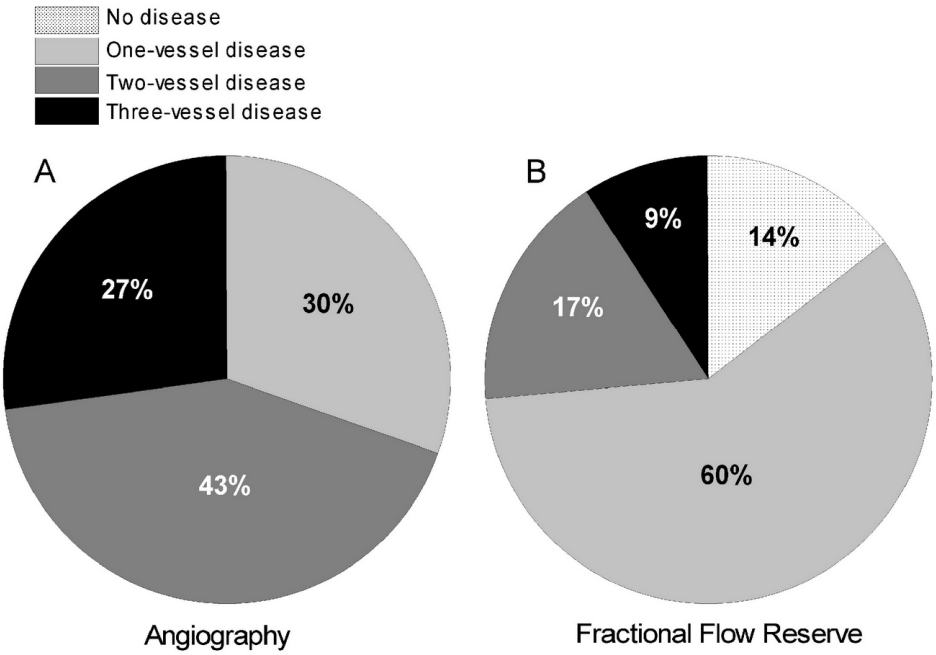

Figure 6. Number of vessel evaluated by angiography alone or with fractional flow reserve. The number of functional diseased vessels can change markedly from the initial angiographic assessment. VD, vessel disease. Reproduced with permission from Sant'Anna et al, Am J Cardiol 2007;99:504–508)

In SYNTAX II trial [66]physiological assessment was performed in 75.5% of the lesions. Out of 1559 lesions (3.49 ± 0.97 lesions per patient) initially intended to be treated based on the angiographic findings 31% of stenoses were deferred and patients with the need of 3VD PCI are only 37.2%, a great minority in comparison with SYNTAX I population (**figure 7**)[67,68].

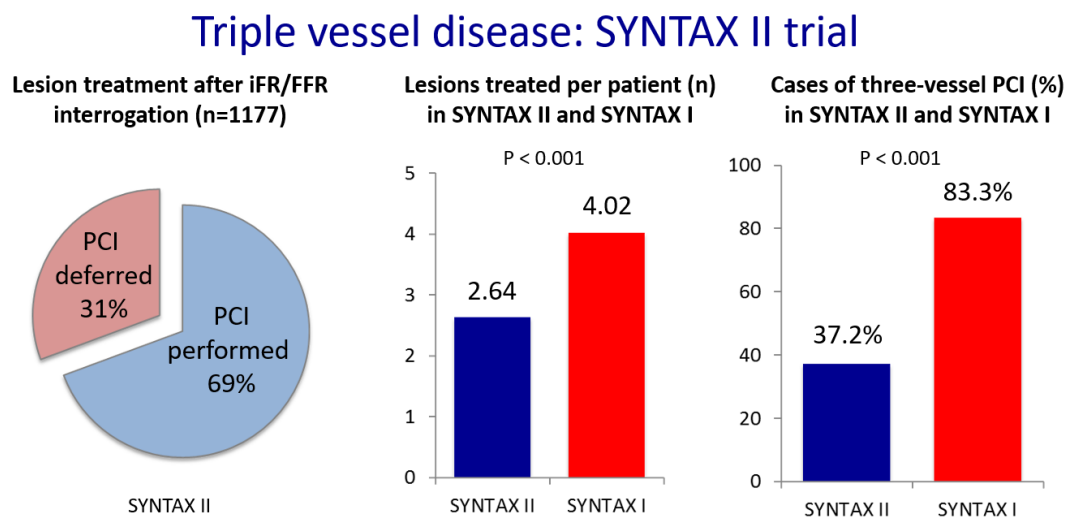

Figure 7. Schematic report of triple vessel disease management in SYNTAX II vs SYNTAX I trial

Consequently, in case of MVD the use of physiology results of paramount importance in order to avoid unnecessary revascularizations. NHPRs indices constitutes an alternative to FFR interrogation in such situation. However, some institutions do not still have access to this technology mainly because as already mentioned above, each commercially available NHPRs using an independent calculation algorithm require a dedicated guidewire and console supplied by the vendor. In these cases, the only indices universally available in any pressure-wire console are the resting Pd/Pa ratio and the FFR. Consequently, a combination of Pd/Pa ratio and FFR could be an alternative to FFR. Previous studies performed by others groups proposed an hybrid Pd/Pa-FFR algorithms obviating the need for vasodilator drugs in more than half of patients (47%) whilst maintaining high classification agreement with an FFR-only strategy[69]. As mentioned above, some authors proposed the use of the so called contrast FFR (cFFR). It is universally available being calculated as Pd/Pa after the induction of submaximal hyperaemia using an intracoronary injection of standard radiographic contrast medium. cFFR has been reported to have a good correlation with FFR, even superior than Pd/Pa ratio[21,70] leading to further reduction in adenosine requirement when combined with FFR.

In summary, being MVD in stable patients a common finding in daily practice, alternative ways to circumvent the need for adenosine or simplify multiple lesions assessment in cath-lab are

still valid to increase adoption of physiology. This topic has been addressed in one of the article included in the present thesis and will be further discussed below (**Part II, 2.1.2**).

3.4.2 Left Main Coronary Artery Disease

LMCA disease is prevalent, occurring in 4% to 9% of patients undergoing coronary angiography[71]. Several studies have highlighted the inadequacies of coronary angiography in the assessment of intermediate LMCA stenosis[72] suggesting use of other modalities to determine LMCA stenosis severity.

Presence of significant LMCA disease (stenosis greater than 50%), is associated with a poor prognosis in the medium term. Studies prior to coronary revascularization showed a survival of less than 40% at 4 years after diagnosis[73].

Limitations of the angiographic evaluation of the severity of the lesions are well established[74] making angiographic evaluation of LMCA stenosis difficult and could be summarized as follows:

- Catheter related issues like catheter-induced spasm or catheter overlap with the LMS, resulting in contrast medium spill over and incomplete mixing of blood and contrast medium in the proximal part of the LMCA
- Angulated LMCA making difficult the interpretation of coronary lesions;
- Lack of a reference segment in cases of diffuse disease or in case of ostial or very distal location of the LMCA stenosis
- Location prone to vessel foreshortening
- Overlapping with Left Anterior Descending (LAD)/Left Circumflex (LCX) branches
- Eccentric lesions
- Reflux of contrast in aortic sinus obscuring ostial lesions
- "Reverse tapering" (smaller calibre at the ostium than in the distal segment, withour atherosclerosis)

Before considering revascularization in a patient with a LMCA lesion, especially if the lesion is ostial, it is important to determine if the lesion really needs to be revascularized. Due to their anatomical location, artifacts induced by the catheter or the severity of distal lesions, interpretation of the LMCA lesions are those that present greater intra- and interobserver variability compared to those located in the rest of the coronary tree. In the CASS (the Coronary

Artery Surgery Study) registry, when stenosis ≥50% was reported, a second observer reported that the stenosis was not significant in 19% of cases[75].

In the case of intermediate stenosis, intravascular imaging or functional assessment have been proposed to identify those patients who could benefit from revascularization.

The reliability of FFR for simple lesions is rarely an issue, but an understanding of FFR for complex LM stenoses with additional lesions in the left anterior descending (LAD) and/or circumflex artery (Cx) branches requires the operator to have a more in-depth appreciation of the physiology as applied in this important anatomic subset.

A simple, isolated LM stenosis is easily assessed by FFR in the routine fashion. One caveat to increase reliability is that ostial FFR assessment requires that the guide catheter be removed from the ostium while infusing intravenous adenosine to avoid the artifact of guide catheter pressure damping. A distal LM stenosis involving the bifurcation of the LAD and LCX can be assessed with two FFR measurements, one in the LAD and another with the pressure wire in the LCX. However, interpreting the FFR in the presence of significant downstream branch lesions, such as a LAD stenosis, is more complicated. This is because the LMCA and LAD lesions act like serial lesions, and the true flow across the LMCA is potentially reduced by a severe downstream stenosis, artifactually elevating the FFR value when measured in the unobstructed vessel.

Available data on Fractional Flow Reserve use in LMCA intermediate stenosis

No definitive data on the prognostic value of physiology measurements in intermediate stenosis (30-70%) of the LMCA are to date available. The presence of significant stenosis (> 70%) on coronary angiography was an exclusion criterion in the DEFER, FAME and FAME II studies, in the same way as in the DEFINE FLAIR study. Only the IFR SWEDEHEART study included 30 patients with significant LMCA stenosis (1.6% of all included patients). The available data supporting the use of FFR in LMCA lesions derive from few studies summarized in **Table 3**. The cutoff values used in these studies have ranged from 0.75-0.80 and the overall number of patients included is limited.

	FFR-Deferred lesions included (n=345)	**Design / Region**	**FFR cut-off**	**Follow-up duration (months ± SD)**
Bech[76], 2001	54	Prospective, two centers / Europe	0.75	29±15
Courtis[77], 2009	27	Prospective, single center / North America	<0.75 and >0.80 (additional clinical data if FFR was between 0.75 and 0.80)	14±12
Hamilos[78], 2009	38	Prospective single center / Europe	0.8	35±25
Jasti[79], 2004	15	Prospective, single center / North America	0.75	38
Jimenez-Navarro[80], 2004	51	Prospective, single center / Europe	0.75	26±12
Legutko[81], 2005	142	Prospective, single center / Europe	0.75	24
Lindstaedt[82],2006	213	Prospective, single center / Europe	<0.75 and >0.80 (additional clinical data if FFR was between 0.75 and 0.80)	29±14

Table 3. Studies focusing on FFR evaluation in intermediate LMCA stenosis.

Technical aspects in the evaluation of LMCA lesions using a pressure wire:

LMCA interrogations using pressure wire present some challenging in respect to other coronary vessel. Among all, three factors are to be particularly taken into consideration: location of the lesion, hyperemic induction and presence of other significant stenosis distally in the coronary tree. Three possible locations of the lesions are anatomically differentiated, depending on whether they affect the ostium, the body or the distal portion (bifurcation). In the same way that the location of the lesion has implications in terms of percutaneous treatment, it has implications for the study with a pressure guide. When the lesion is located in the ostium or in the body, it is essential that the coronary catheterization be coaxial. Non-coaxial catheterization involves contact of the catheter lumen with the vessel wall so that it can dampen aortic pressure by artificially raising the FFR value. For this reason, non-selective catheterization is recommended both when equalizing or normalizing the catheter and guideline pressures and when the guide is placed distal to the lesion to perform the FFR measurement at the time of maximum hyperemia. Therefore, interrogation of ostial lesion may imply this additional factor potentially influencing measurement. When the lesion is located in the distal part of the LMCA and affects the origin of its main branches, it is recommended to approach the distal LMCA and each one of its branches as a functional unit, regardless of the degree of involvement of each one. For the calculation of the

FFR, the measurement is made from the anterior descending and from the circumflex and the LMCA lesion is considered to be functionally significant when the measurement from any of the two main vessels is less than 0.80.

Use of intracoronary bolus of adenosine is not recommended because, if a non-selective catheterization of the left coronary is necessary, part of the medication administered does not go to the coronary, leading to a suboptimal hyperemic state. For this reason, intravenous drug administration is recommended, either adenosine (dose from 140 micrograms / kg / min infused for at least two minutes.

The presence of isolated LMCA lesion is infrequent. A series of unselected patients who underwent diagnostic coronary angiography showed that in patients with TCI involvement, only 9% had a single lesion in the TCI; 17% had a TCI lesion and involvement of 1 vessel; 35% had TCI injury and two vessels and 38% had TCI disease and 3 vessels[83]

. The presence of lesions in the anterior descending and / or circumflex can affect the measurement of the FFR in the LMCA, so it is recommended to put the pressure guide in the artery that does not present injuries. However, a lesion in the anterior descending artery may affect the determination of the FFR with the guide in the circumflex because the flow through the LMCA depends on the flow in the anterior descending and in the circumflex, and an injury in the anterior descending artery could decrease the flow in the LMCA and artificially raise the FFR value. The influence of distal lesions on LAD / LCX in the measurement of the FFR will depend on the severity of the lesion and the myocardial mass supplied by the affected vessel. In an experimental study with an animal model, it was shown that the measurement of FFR in the LMCA in the presence of distal lesions is possible, positioning the guide in a vessel without injury. The presence of distal lesions leads to overestimation of the FFR, so a value <0.75 will indicate that treatment is necessary regardless of the presence of distal lesions. In this experimental study, it was observed that FFR values > 0.80 were only obtained when the injury in the distal vessel was very severe (combined FFR <0.50) and was located in the most proximal portion[84] (**Figure 8**).

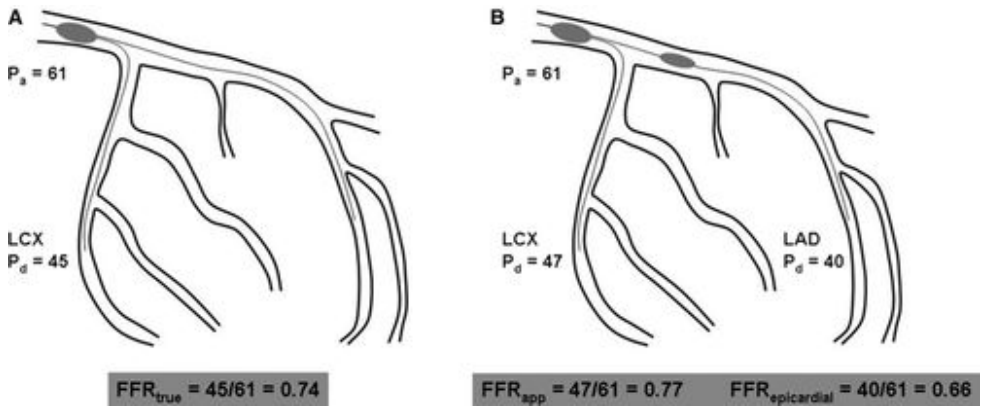

Figure 8. Schematic example of physiological measurements. A, True fractional flow reserve (FFRtrue) of the left main coronary artery obtained during left main balloon inflation and no stenosis in the left anterior descending (LAD) artery (FFRtrue=distal pressure [Pd]) in the left circumflex (LCX) artery divided by proximal arterial pressure (Pa). B, FFRapp obtained during balloon inflation in the LAD (FFRapp=LCX Pd/Pa during downstream balloon inflation). FFRepicardial represents FFR of left main plus LAD (FFRepicardial=LAD Pd/Pa during LAD balloon inflation). Reproduction with permission from Andy S.C. Yong. Circulation: Cardiovascular Interventions. Fractional Flow Reserve Assessment of Left Main Stenosis in the Presence of Downstream Coronary Stenoses, Volume: 6, Issue: 2, Pages: 161-165

Use of intravascular ultrasound imaging in LMCA intermediate stenosis

The IVUS allows obtaining a real-time tomographic image of the light and the coronary artery wall so that the luminal area, the composition and distribution of the plaque and the actual size of the vessel can be assessed **(Figure 9**). Differently from FFR, it allows to disclose atherosclerotic plaque with unstable characteristics, ulcerations and to quantify the plaque burden. In addition, after the stent is implanted, it allows evaluating the adequate expansion and apposition to the coronary wall of the stent and can be especially useful in the case of treatment of bifurcation lesions to decide the need to implant a second stent. In patients with LMCA involvement, observational studies and meta-analyses suggest that IVUS-guided stent implantation is associated with a better clinical evolution during follow-up (33-35).

Thus, the guidelines on revascularization of the European Society of Cardiology recommend IVUS to assess severity and guide treatment in patients in whom LMCA is to be treated percutaneously with a grade IIA indication (3). Beyond the impact in optimizing stent implantation, only 5 studies encompass use of IVUS to defer intermediate stenosis. (**Table 4**).

	IVUS-Deferred lesions included (n=563)	**Design / Region**	IVUS cut-off	Follow-up lenght (months ± SD)
De La Torre Hernandez (LITRO)[85], 2011	179	Multicenter, prospective / Europe	6	24
De la Torre Hernandez[86], 2007	48	Single-center, prospective /Europe	6	40±17
Fassa[87], 2005	114	Retrospective / North America	7.5	43.2
Okabe[88], 2008	100	Single center, prospective (only deferred lesion) / North America	Clinicians decision	31.5±17
Abizaid[72], 1999	122	Single center, prospective / North America	Clinicians decision	11.7

Table 4. Studies focusing on IVUS evaluation on intermediate LMCA stenosis.

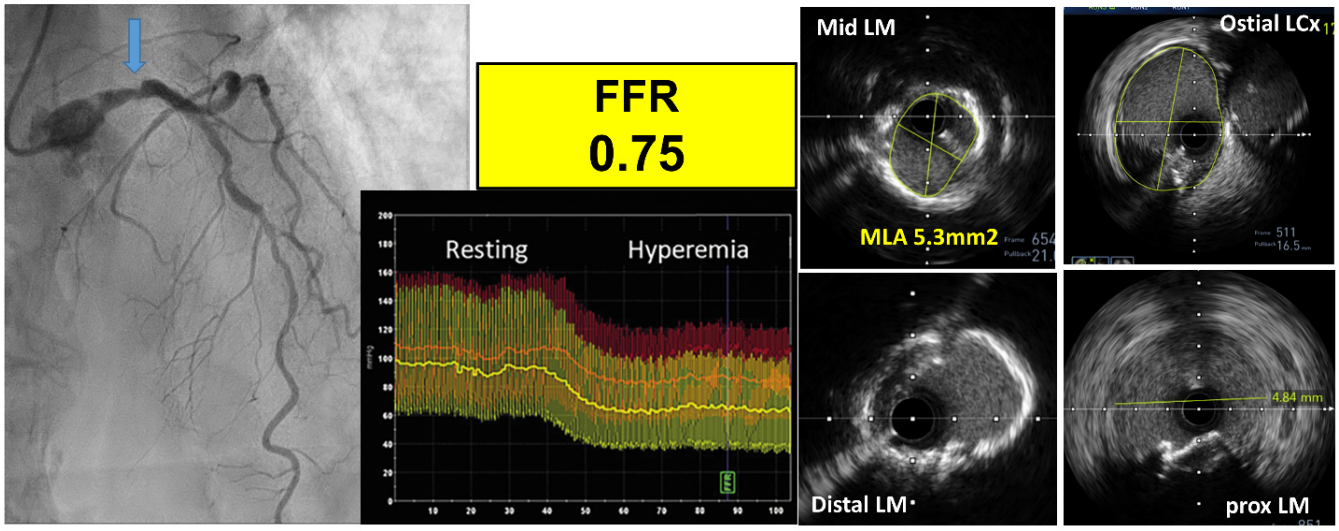

Figure 9. Integrated intravascular Ultrasoung Imaging (IVUS) and Fractional Flow Reserve (FFR) evaluation of intermediate stenosis of Left Main in a stable clinical setting. Red and yellow curves indicate mean of Aortic Pressure (Pa) and Distal Pressure (Pd), respectively. This case presented a remarkable decrease of pressure gradient with a significant reduction in Minimal Lumen Area at IVUS interrogation according to the most adopted cut-off of 6.0mm2. Reproduction with permission Cerrato E. and Varbella F, Live case, GISE 2020, Rome, Italy

Minimal Lumen Area (MLA) derived from IVUS was used to define a cut-off for treatment. However this remain to date debatable because it seems to be population dependent and ethnicity related as we can suspect looking how different is the average LMCA-MLA in the study of Fassa[87] performed in North America (7.6 mm^2), compared to the study from Park[89] performed in Korea (4.8 mm^2). The dynamic relationship between lesion length, MLA (by IVUS), and FFR remains

still under investigation. Following this argument, it is likely that longer, diffuse lesions with larger IVUS-derived MLA might be ultimately found to harbour greater physiological significance than short, focal lesions with lesser MLAs.

Summarizing available evidence, we still have few data (and no RCT) available regarding these two adjunctive invasive diagnostic tools, recommended in clinical guidelines for ambiguous LMCA assessment. For this reason, the safety of intermediate LMCA stenosis revascularization deferral based on FFR and IVUS is one of the topic addressed in the present thesis (**Part II, 2.1.1**)

3.4.3 Acute Coronary Syndrome

The value of FFR to guide revascularization of non-culprit stenoses in the setting of ACS is less well established. MVD is present in 40% of patients with Acute Coronary Syndrome with ST Segment Elevation (ACS-STEMI) [90]and up to 70% of patients with Acute Coronary Syndrome with non-ST Segment (ACS-NSTE)[91,92]

While in case of ACS-STEMI the identification of culprit artery is usually straightforward following information from electrocardiogram and coronary angiography, in ACS-NSTE identification of culprit lesions might be challenging inducing the interventional cardiologist in using others tools like intracoronary imaging or physiology to be helped in the decision-making process upon revascularize or not a vessel. With the growing adoption of coronary physiology, FFR is also increasingly being used in this context to guide revascularization in patients with ACS, particularly to assess the functional relevance of non-culprit lesion (NCL) in patients with MVD. Available evidence, including RCTs[93,94], supports the use of FFR guidance in ACS NCL compared with culprit only treatment. Moreover, FFR utilization has demonstrated better outcomes with respect to angiography-alone approaches in both ACS or SAP[95].

In **Table 5** were reported RCTs investigating benefit of MVD revascularization vs culprit-only revascularization in the setting of STEMI.

Trial	Year	N	Follow-up	Primary endpoint	Primary endpoint in complete vs culprit-only rev. group	HR (95% CI)	Comment
PRAMI[96]	2013	465	23m (mean)	Cardiac death, non-fatal MI or refractory angina	9.0% vs.23.0%	0.35 (0.21-0.58)	Angio guided
CvLPRIT[97]	2015	296	12m	All-cause death, recurrent MI ischemia-driven revascularization, and heart failure	10.0% vs.21.2%	0.45 (0.24-0.84)	Angio guided
DANAMI-3-PRIMULTI[93]	2015	627	27m (median)	All-cause death, non-fatal MI and ischemia-driven revascularization of non-infarct related arteries	12.0% vs.22.0%	0.56 (0.38-0.83)	FFR guided PCI of NCL
COMPARE-ACUTE[94]	2017	885	12m	All-cause death, non-fatal MI revascularization, and cerebrovascular events	7.8% vs.20.5%	0.35 (0.22-0.35)	FFR-guided PCI of NCL
COMPLETE[98]	2019	4041	3yrs	Cardiovascular death or MI	7.8% vs.10.5%	0.74 (0.60-0.91)	Angio guided PCI or NCL (<1% of cases psysiology performed in intermediate stenosis)

Table 5. Current evidence of complete versus culprit lesion only revascularization in patients with ST-segment elevation myocardial infarction and multivessel disease; m: months; yrs: years.

In particular, two RCTs – PRAMI (Preventive Angioplasty in Acute Myocardial Infarction) and CVLPRIT[97] (Complete versus Lesion-Only Primary PCI) - reported a beneficial long-term effect of complete vs culprit-only revascularization on the basis of an angio-only approach. Recently the Complete vs Culprit-only Revascularization to Treat Multi-vessel Disease after Primary PCI for STEMI (COMPLETE) trial[98] confirmed these findings with the largest sample size currently available (n=4041), indicating a benefit in terms of reduction of MI when revascularization was performed in NCL. Again, angiography was used to judge the severity of bystanders stenoses and adoption of intracoronary physiology was mandatory only in intermediate

stenosis occurring, overall, in less than 1% of the cases. Previous studies using FFR to guide complete revascularization in patients presenting with STEMI, such as DANAMI-3-PRIMULTI[93] and COMPARE-ACUTE[94], cannot be used to clarify this issue given the absence of a SAP comparator group and also for their relative limited sample size. In a recent meta-analysis[99] of individual patient data including those two RCTs as well as FAME 2 trial[100] (encompassing only SAP patients), FFR-guided PCI resulted in a reduction of the composite of cardiac death or MI compared with medical therapy in SAP, which was driven by a decreased risk of MI.

In the setting of ACS-NSTE, two clinical studies were conducted to assess the value of FFR: a subanalysis of FAME[95] and the Fractional Flow Reserve Versus Angiographically Guided Management to Optimise Outcomes in Unstable Coronary Syndromes (FAMOUS NSTEMI) trial[101]

FAME enrolled 328 patients with ACS-NSTE (negative troponin) and MVD out of total of 1005 were included. The benefit of an FFR-guided PCI was similar to that observed in SAP group with a 5% of absolute risk reduction at 2 years of the combined endpoint of death, MI or any revascularization. However, being a substudy it was not powered to detect superiority of FFR in ACS NCL and neither the target lesion interrogated (culprit vs NCL) nor the event rate in deferred lesions by FFR was reported.

Some years later, the FAMOUS NSTEMI randomized 350 patients with NSTEMI with at least one coronary stenosis of ≥30% severity by visual assessment of either FFR-guided versus angiography-only approach. For the primary outcome, the proportion of patients treated initially by medical therapy was higher in the FFR-guided group than in the angiography-guided group (22.7% vs.13.2%, p = 0.022). At 12 months, revascularization remained lower in the FFR-guided group (79.0 vs. 86.8%; p = 0.054). However, has to be noted that percentage of intermediate stenosis (50-70% at visual assessment) included was about 20% and the median time from the index episode of myocardial ischaemia to angiography was quite long (3 days). Interestingly all MACE occurred in the group of patients deferred on the ground of FFR (7.5% vs 0%).

Accordingly, it remains inconclusive if physiology guided revascularization in patients with ACS and MVD will be associated with an even lower event rate than anatomic guided PCI (as has already demonstrated in the context of SAP) and overall, few data are available regarding the

comparative performance of FFR in ACS versus SAP settings. Studies performed to date are underpowered or not specifically designed to answer this clinical question. While some studies support the reliability of FFR measurements in ACS patients, a number of studies have consistently reported poorer clinical outcomes in patients in whom revascularization was deferred based on FFR measurements, both with respect to previously published data collected in SAP and in the case of direct comparison with a SAP group (**Table 6**).

Trial	Comparison group	Number of patients (PCI deferred)	Follow-up	Outcome	FFR cut-off used
Hernández Garcia et al[102]	None (ACS only)	24 UA/NSTE 19 recent MI	10.7m (mean)	Recurrent ACS >11.6%	0.75
Fischer et al[103]	ACS vs. SAP	35 ACS vs 65 SAP	12m	MACE: 28% ACS vs 17% SAP	0.75
Lopez-Palop et al[104]	None (ACS only)	106 ACS	12m	MACE: 7.5%	0.75
Mehta et al[105]	ACS vs. SAP	334 ACS vs 340 SAP	54m (mean)	MACE: 32% ACS vs.23% SAP	0.80
Hakeem et al[106]	ACS vs. SAP	206 ACS vs 370 SAP	41m (mean)	MACE: 23% ACS vs. 11% SAP	0.80
Picchi et al[107]	None (ACS only)	319 ACS	36m	MACE: 12%	0.80

Table 6. Summary of main studies evaluating revascularization deferral based on FFR in Acute Coronary Syndrome (ACS). MACE: Major Adverse Cardiovascular Events. SAP: Stable Angina Pectoris

Heterogeneity in inclusion criteria, endpoints and follow-up suggest the need for a larger clinical trial with homogeneous time of assessment, and clear definition of the vessel interrogated by FFR preventing to draw firm conclusions.

Consequently, the accuracy of FFR during ACS still deserves further investigation and will be the object of this thesis (**Part II, 2.1.3**)

3.4.4 Diabetic patients

The incidence of T2DM continues to rise[108] and has quickly become one of the most prevalent and costly chronic diseases worldwide. A close link exists between T2DM and cardiovascular disease (CVD), which is the most prevalent cause of morbidity and mortality in diabetic patients. The relative risk for CVD morbidity and mortality in adults with T2DM is three-fold higher in men and two-fold higher in women compared to those without T2DM[109]. Although, over the last

two decades, cardiovascular mortality has declined considerably in the general population, a similar trend has not been observed amongst diabetic patients. Cardiovascular risk factors such as obesity, hypertension and dyslipidemia are common in patients with DM, placing them at increased risk for cardiac events. In addition, many studies have found biological mechanisms associated with T2DM that independently increase the risk of CVD in diabetic patients[110].

T2DM is associated with a significant increase in the risk of CAD[111] both acutely and at long term follow up after coronary revascularization. As the prevalence of T2DM is estimated to double in the next ten years, the burden of cardiovascular disease associated with this condition will dramatically increase[112].

One of the mechanisms that may be related to this inferior outcome is the higher prevalence of periprocedural myocardial infarction (PMI) after PCI observed in T2DM patients, which has been associated with endothelial dysfunction, pro-thrombotic state, chronic microvascular dysfunction, increased atheroma burden, vessel wall inflammation, and development of vulnerable plaques prone to distal embolization[113].

Antiplatelet agents, in particular Ticagrelor, might play a protective role in this setting. Ticagrelor, is different to Clopidogrel and other P2Y12 inhibitors, as it reduces the physiological clearance of adenosine by inhibiting its cellular uptake, thus increasing the plasma concentration of adenosine. As the primary aim of adenosine is achieving tonic and cellular protection during stress conditions[114], adenosine in turn may protect the myocardium from both ischemic and reperfusion injuries via its potent vasodilator effect and possibly by anti-inflammatory and antiplatelet properties[115]. Additionally, previous research[116] has identified a more pronounced effect of adenosine on microcirculatory resistance in patients with obesity and diabetes. Therefore, a potentially higher protective effect of Ticagrelor during PCI might be expected in this subgroup.

From a clinical perspective, a large RCT[117] recently demonstrated a lower incidence of ischemic cardiovascular events in patients with SIHD and DMT2 treated with Ticagrelor vs Clopidogrel.

3.5 Introduction of the doctoral thesis

Following all the achievements described above, clinical practice guidelines[26,118] recommend the use of coronary physiology to decide if revascularization of intermediate-severity coronary stenosis is indicated. Physiology is also increasingly being used to guide revascularization in

specific subset of patients with complex anatomical or clinical setting such the case of LMCA, MVD or in the setting of ACS. In this context use of physiology still has some uncertainties or is currently under investigation in order to obtain a more extensive data on clinical outcome. At this regards, this doctoral thesis brings together three original research articles published in international scientific journals exploring the advantages and limitation of using the FFR in such complex scenarios providing consistent new data in particular in the setting of FFR-guided revascularization or deferral of revascularization of NCL after ACS, reporting the result of the larger available database of individual data from Spain, Portugal, Sweden, France, England and South Korea.

The second part of the thesis sought to underscore the importance of the coronary microcirculation. Firstly, a review paper focused on the importance of multimodal physiology to evaluate microcirculatory dysfunction summarizing the different modality available for the real-time assessment of microvasculature especially in the setting of ACS. Therefore, novel data regarding potential capacity of specific drugs in improving microcirculatory status or providing protection during PCI in the high-risk subset of T2DM patients were discussed. On the matter of fact, the abnormal coronary microcirculation along with the higher risk of periprocedural microcirculatory damage in patients with T2DM represents one of the harmful and still unmet issues potentially connected with a poor long-term outcome[119,120]. New antiplatelet agents, in particular Ticagrelor, might play a protective role in this setting increasing the plasma concentration of adenosine protecting the myocardium from both ischemic and reperfusion injuries via its potent vasodilator effect and possibly by anti-inflammatory and antiplatelet properties[115]. Regarding this topic, the design and the results of the original randomized multicenters clinical trial PREDICT (PRotective Effect on the coronary microcirculation of patients with DIabetes by Clopidogrel or Ticagrelor) was provided in the last part of the thesis. PREDICT trial was designed and conducted in three Spain Institutions during the doctoral period.

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PART II

1. OBJECTIVES OF THE THESIS

The main purposes of the present thesis are the followings:

a. to test alternative ways to circumvent the need for adenosine and increase the adoption of physiology to guide revascularization in case of multivessel / multilesion stenosis. In particular, to test different multi-step hybrid algorithms (Pd/Pa-FFR; cFFR-FFR and a novel Pd/Pa-cFFR-FFR) in terms of agreement with an FFR only-strategy evaluating the proportion of patients free from adenosine and additional medium contrast administration;
b. to perform a comprehensive systematic review and study-level meta-analyses of available studies in which FFR and IVUS were used to decide upon LMCA disease, to critically appraise, the long-term safety of their use for revascularization deferral;
c. to assess the reliability of the FFR to guide therapeutic decisions in patients with ACS and multivessel disease investigating the safety of revascularization deferral of nonculprit lesions performing a patient-level meta-analysis of data coming from three multinational registries and two randomized-clinical trials.
d. to review several proposed methods to allow intravascular quantification of microvasculature, exploring different domains and summarizing these techniques along with the prognostic information provided by each modality;
e. to explore the microcirculatory domain in high-risk patients such those with T2DM;
f. to design and perform a multicenter, open-label, randomized clinical trial with two arms to compare the effect of Ticagrelor (an antiplatelet drug that increase the circulating levels of adenosine) over Clopidogrel on the coronary microcirculation during PCI in patients with T2DM or rather to document changing in coronary microcirculatory resistance caused by treatment onset and caused by PCI.

2. MATERIALS, METHODS AND RESULTS OF THE THESIS

2.1. Implementation of Coronary Physiology in complex clinical and angiographic scenarios

2.1.1. Publication No. 1, original article

"Simplified hybrid algorithms for pressure wire interrogation exploiting advantages of a baseline and contrast Pd/Pa ratio indexes to predict stenosis significance: Insight from the SPARE multicenter prospective study"

Cerrato E, Tomassini F, Salinas P, Pavani M, Conrotto F, Echavarria-Pinto M, Macaya F, Quadri G, D'Ascenzo F, Quirós A, Varbella F, Escaned J.

Catheter Cardiovasc Interv. 2018 Nov 15;92(6):1090-1096. doi: 10.1002/ccd.27616. Epub 2018 Apr 23. PMID: 29683558.

Summary: with the advent of drug eluting stents the likelihood of restenosis after PCI decreased markedly allowing to safely treat with stents multiple stenoses. However, invasive assessment of coronary vessels has to be performed in such in order to properly identify perfusion-limiting stenosis, minimize risks, complication and optimize health care costs. In this scenario both hyperemic and NHPRs demonstrate to be safe and effective in delivering consistent patient outcomes at one year of follow-up and are consequently recommended in current European Guidelines[1] to assess intermediate stenoses in SAP. However, worldwide adoption of FFR remains low in everyday practice. This can be due in part to the prerequisite to achieve a maximal hyperemia for FFR calculation, which is time-consuming, expensive and requires the use of potent vasodilators. Besides, iFR or others NHPRs may be not available in all catheterization laboratories requiring a dedicate console. Given these assumptions the objectives of the SPARE (Simplified hybrid algorithms for pressure wire interrogation exploiting advantages of a baseline and contrast Pd/Pa ratio indexes to predict stenosis significance) multicenter study were to evaluate the merits of a hybrid algorithms that combines the translesional pressure ratio (Pd/Pa) obtained at rest, after contrast medium injection (cFFR) and after adenosine administration (FFR). We tested the

efficiency of three different multi-step strategies combining the three indices to classify stenosis severity, using FFR-only measurement as reference. All three different hybrid algorithms (Pd/Pa-FFR; cFFR-FFR; Pd/Pa-cFFR-FFR) have more than 95% of agreement with FFR. Yet, we proposed a novel multistep hybrid approach including Pd/Pa-cFFR-FFR that demonstrated the best performance, avoiding the need of adenosine and medium contrast in 90% and 48% of cases, respectively.

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ORIGINAL STUDIES

WILEY

Simplified hybrid algorithms for pressure wire interrogation exploiting advantages of a baseline and contrast Pd/Pa ratio indexes to predict stenosis significance: Insight from the SPARE multicenter prospective study

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Abstract

Background: Simplification of functional stenosis assessment with pressure guidewires may facilitate adoption of physiology-guided revascularization. An important step in this regard is the avoidance of hyperemic agents, required for fractional flow reserve (FFR) calculation. We evaluate the merits of a hybrid algorithms that combines the translesional pressure ratio (Pd/Pa) obtained at rest, after contrast medium injection (cFFR) and after adenosine administration (FFR).

Methods and Results: Eighty-six patients with 108 de novo intermediate coronary stenoses were included in this prospective, multicenter study. Using prespecified cut-off values that correctly identified stenosis with a 95% of agreement (<0.89 and >0.96 for Pd/Pa; <0.84 and >0.87 for cFFR) we tested the efficiency of three different multi-step strategies combining the three indices to classify stenosis severity, using FFR-only measurement as reference. All three different hybrid algorithms (Pd/Pa-FFR; cFFR-FFR; Pd/Pa-cFFR-FFR) have more than 95% of agreement with FFR. Yet, the novel Pd/Pa-cFFR-FFR hybrid strategy demonstrated the best performance, avoiding the need of adenosine and medium contrast in 90% and 48% of cases, respectively.

Conclusions: A hybrid Pd/Pa-cFFR-FFR decision-making algorithm could be an alternative and valuable strategy to increase the adoption of a physiology-guided PCI using conventional pressure guidewires and consoles.

KEYWORDS
cFFR, CMR, FFR, hybrid algorithms, percutaneous coronary interventions, resting Pd/Pa

1 | INTRODUCTION

Based on available evidence [1–4] physiological assessment with fractional flow reserve (FFR) is currently recommended in the Guidelines to properly select patients that may benefit from coronary revascularization. However, worldwide adoption of FFR remains low in everyday practice. This can be due in part to the prerequisite to achieve a maximal hyperemia for FFR calculation, which is time-consuming, expensive and requires the use of potent vasodilators, in occasions not available or without an on-label indication for this purpose [5].

Recently, data from the DEFINE FLAIR and iFR Swedeheart trials [6,7] have demonstrated that a nonhyperemic, resting indices like

Abbreviations: Pd, distal coronary pressure; Pa, aortic pressure; FFR, Fractional Flow Reserve; iFR, instantaneous wave-Free Ratio; CMR, cFFR: contrast medium induced Pd/Pa ratio; PCI, percutaneous coronary intervention.

iFR-guided strategy constitutes an alternative to FFR interrogation, delivering consistent patient outcomes at one year of follow-up while significantly reducing patient discomfort, procedural time, and costs.

However, the iFR technology is not still available in all catheterization laboratories, limiting its use as an alternative to FFR in current practice. Thus, alternative ways to circumvent the need for adenosine are still valid to increased adoption of physiology.

Given these assumptions the objectives of the "SimPlified Hybrid Algorithms for pressure wire interrogation exploiting advantages of a baseline and contrast Pd/Pa ration index to predict stenosis significance: insight from the SPARE multicenter prospective study", were:

> (i) to test and compare the accuracy of Pd/Pa and contrast medium injection (cFFR) to FFR; (ii) to test the agreement between an FFR-only strategy and both the previously proposed hybrid Pd/Pa-FFR [8] and cFFR-FFR [9] algorithms; and (iii) to test and compare the efficiency of three different multi-step hybrid algorithms (Pd/Pa-FFR; cFFR-FFR and a novel Pd/Pa-cFFR-FFR) in terms of agreement with an FFR only-strategy (cut-off value of ≤0.80) evaluating the proportion of patients free from adenosine and additional medium contrast administration.

2 | METHODS

From September 2015 to November 2016, among all patients referred for a diagnostic catheterization for a suspected coronary artery disease, consecutive patients with angiographically intermediate (diameter stenosis 30% to 80% at visual estimation) stenoses were prospectively enrolled in three centers in Europe. Left main and right coronary ostium stenoses, severe renal failure (Cockroft-Gault glomerular filtration rate ≤30 mL/min), recent myocardial infarction (within one week) or prior myocardial infarction in the area of myocardium subtended by target vessel, severe valvular heart disease, acute or chronic decompensated heart failure and a known history of Asthma or COPD with severe obstructive component were exclusion criteria.

Participating centers were San Luigi Gonzaga University Hospital, Orbassano and Infermi Hospital, Rivoli, Rivoli (Turin), Italy; University of Turin, Città della Salute e della Scienza, Turin, Italy; and Hospital Clínico San Carlos, Madrid, Spain. List of other site investigators is available in Supporting Information.

2.1 | Procedure

Femoral or radial approach were used at operators' discretion. Non-ionic radiographic contrast medium was used for all patients (Iomeron; Bracco, Milan, Italy). Every coronary lesion was assessed by multiple orthogonal projections and visually assessed by two independent expert reviewers. After i.v. administration of heparin 100 IU/kg or bivalirudin a pressure guidewire was advanced. Resting Pd/Pa, cFFR and FFR were measured following a standard procedure following a methodology described below. In particular, cFFR was calculated as the ratio of distal coronary pressure divided by aortic pressure obtained after achievement of submaximal hyperemia with a single injection of radiographic-contrast medium. A femoral or a large brachial vein was used for systemic administration of adenosine. An FFR value of ≤0.80 was considered the significant ischemic threshold. In any case, beyond the purpose of this study, clinical decisions among revascularize or not where finally taken according to the FFR result.

2.2 | Protocol for indexes assessment

0.2 mg of i.c. isosorbide dinitrate was administered before starting measurements.

Three sequential steps were performed separated by at least 30 sec until the return of Pd/Pa ratio to baseline value:

1. Resting Pd/Pa assessment;
2. cFFR assessment: a single injection of 6 mL of radiographic contrast medium Iomeron at a flow of 4 mL/sec and at a pressure of 300 psi was performed using a power injector system (Acyst, Bracco) registering the minimal cFFR value. The injection of contrast medium was followed by saline flushing of the guiding catheter to avoid pressure damping due to contrast medium viscosity;
3. FFR assessment: FFR was measured during maximal hyperemia induced by i.v. adenosine administration (140 mcg/kg/min).

2.3 | Study endpoints

Study endpoints were:

1. Diagnostic accuracy of Resting Pd/Pa, and cFFR in predicting FFR≤0.8 as measured by area under the curve (AUC) by ROC curve for each different technique.
2. Compare the predicted result of the following hybrid strategies in terms of agreement with an FFR only-strategy (cut-off value of ≤0.80) evaluating the proportion of patients potentially free from adenosine and additional medium contrast administration:
   a. Hybrid Pd/Pa-FFR Strategy: Using deferral Pd/Pa value of >0.96 and a treatment Pd/Pa value of <0.89, only stenoses with a Pd/Pa value between 0.89 and 0.96 will be tested with FFR according to the algorithm previously proposed [8].
   b. Hybrid cFFR-FFR Strategy: Using deferral cFFR value of >0.87 and a treatment cFFR value of <0.84, only stenoses with an equivocal cFFR value between 0.84 and 0.87 will be tested with FFR according to the algorithm previously proposed by Leone et al. [9].
   c. Hybrid Pd/Pa-cFFR-FFR Strategy: we proposed this novel two-step algorithm. First, resting Pd/Pa will be performed to all stenoses using deferral Pd/Pa value of >0.96 and a treatment Pd/Pa value of <0.89. Then, stenoses with an equivocal Pd/Pa value between 0.89 and 0.96 will be tested with cFFR, using deferral cFFR value of >0.87 and a treatment cFFR value of <0.84. Finally, only in case of an equivocal cFFR value between 0.84 and 0.87, stenoses will be tested with FFR using 0.80 as cut-off (See **Figure** 1)

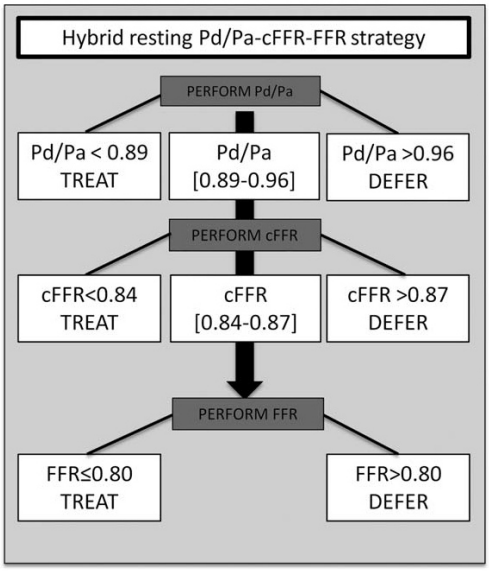

FIGURE 1 Hybrid iFR-cFFR-FFR strategy

Angina-like sensation, dyspnea, flushing or development of complete atrium-ventricular block (AVB) or any other complication were carefully recorded.

All data were registered in a dedicated electronic database. Protocol of study was available on our website (http://www.cardiogroup.org).

3 | STATISTICAL ANALYSIS

Continuous variables were presented as mean ± SD or median (1st quartile to 3rd quartile). Categorical variables were presented as counts and percentages. Agreement between indices was described by Bland-Altman plots—together with bias and limits of agreement—and Pearson's correlation coefficient. ROC curve analysis including DeLong test was used to assess the performance of the indices with respect to FFR. Differences were considered significant if $P < .05$ (two-sided). Sample size was calculated assuming a mean Pd/Pa value of 0.90 ± 0.06 and a mean FFR value of 0.83 ± 0.11 (as in the ADVICE II study [8]) and a difference of 0.02 ± 0.02 between cFFR and FFR as the superiority threshold of FFR over cFFR (as reported in the RINASCI study [9]). According to this calculation, at least 104 lesions were required to have the 80% power to identify a significant difference between the different approaches. SPSS 20 (Armonk, NY: IBM Corp.), Graphpad prism 4 (La Jolla, California) and R software (http://www.R-project.org) were used for calculations and graphics.

4 | RESULTS

4.1 | Population

Eighty-six patients with 108 de novo intermediate coronary stenoses were prospectively enrolled.

Demographics and angiographic characteristics are reported in **Table 1**. Most patients were referred for a stable ischemic disease or atypical chest pain, the average angiographic percentage of stenosis was 55.4 ± 7.4, and the most represented target vessels was left

TABLE 1 Baseline and angiographic features

Baseline features	Patient (*n* = 86)
Age, mean ± SD	66.7 ± 9.9
Sex (Male), *n* (%)	69 (80.2)
Weight (kg),mean ± SD	74.5 ± 15.5
Height (cm), mean ± SD	167 ± 11.8
BMI (kg/m^2), mean ± SD	26.0 ± 4.1
Creatinine value (mg/dL) mean ± SD	1.0 ± 0.3
Creatinine clereance (mL/min; Cockroft-Gault) mean ± SD	63.1 ± 16.9
Hypertension, *n* (%)	69 (80.2)
Diabetes mellitus, *n* (%)	30 (34.9)
Hyperlipidemia, *n* (%)	48 (55.8)
Active Smoking, *n* (%)	41 (47.7)
Chronic obstructive pulmonary disease *n* (%)	8 (9.3)
Ejection Fraction mean ± SD	54.2 ± 11.5
Previous cardiovascular history *n* (%) Myocardial infarction Percutaneous coronary intervention Coronary artery by-pass graft Valvular surgery	37 (43.0) 52 (60.5) 1 (1,2) 3 (3.5)
Drugs *n* (%) Aspirin $P2Y_{12}$ Beta-blockers Angiotensin-converting-enzyme inhibitors Calcium-channel blockers RAAS antagonists Statins Diuretics Nitrates	77 (89.5) 56 (65.1) 64 (74.4) 55 (64.0) 19 (22.1) 7 (8.1) 78 (90.7) 36 (41.9) 19 (22.1)
Clinical indication for angiography *n* (%) Stable angina/silent ischemia *n* (%) Acute coronary syndrome *n* (%) Atypical chest pain/others *n* (%)	40 (46.5) 35 (40.7) 11 (12.8)
Access site: radial *n* (%)	73 (84.8)
Multivessel disease *n* (%)	64 (59.2)
Angiographic and procedural features	Stenoses (n = 108)
Target vessel *n* (%) Left anterior descending Left circumflex Right coronary artery	73 (67.6) 18 (16.7) 17 (15.7)
Target segment *n* (%) Proximal Mid Distal	41 (38.0) 47 (43.5) 20 (18.5)
% stenosis visual estimation mean ± SD	55.4 ± 7.4

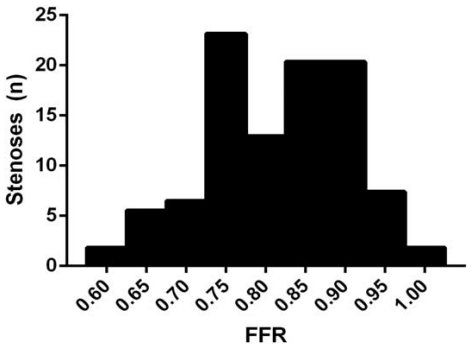

FIGURE 2 Histogram of study population: distribution of FFR values range from 0.60 to 1.0

anterior descending (68%). **Figure** 2 shows the frequency distribution of FFR values, which was unimodally distributed around the FFR cutoff value (mean FFR of 0.81 ± 0.09). All stenoses had an FFR above 0.6 reflecting the daily clinical practice. Overall, stenoses with FFR ≤0.80 were 52.

4.2 | Safety

Baseline Pd/Pa was measured with no symptoms. CFFR assessment by means of medium contrast administration was feasible without any symptoms in all patients. Regarding adenosine administration during FFR assessment, 12 patients (13.9%) complained of mild dyspnea, chest pain and/or facial flushing while 8 developed a transient complete AVB in any case spontaneously reversible except in one case in which 1 mg of i.v. atropine was required.

4.3 | Relationship between indexes

Distributions of values of each indexes are represented in **Figure** 3. Median resting Pd/Pa, cFFR, and FFR values were respectively 0.90 (IQR 0.89-0.97), 0.85 (IQR 0.80-0.92) and 0.82 (IQR 0.75-0.88). Both baseline Pd/Pa ($r = 0.67$, $R^2 = 0.45$; $P < .001$) and cFFR ($r = 0.85$, $R^2 = 0.73$; $P < .001$) showed a significant correlation with FFR (Figure 4) although cFFR demonstrated the strongest correlation with a close agreement at Bland-Altman analysis (0.03 ± 0.05, 95% CI of disagreement: −0.12 to 0.05) (Figure 5). At ROC curve analysis AUC in predicting an FFR value ≤0.80 was 0.89 (95% IC 0.82-0.96) for resting Pd/Pa and 0.96 (95% IC 0.92-0.99) for cFFR (Figure 6). The cFFR threshold of ≤0.84 showed the best accuracy in predicting an FFR value ≤0.80 (Sensitivity 0.93 – Specificity 0.96).

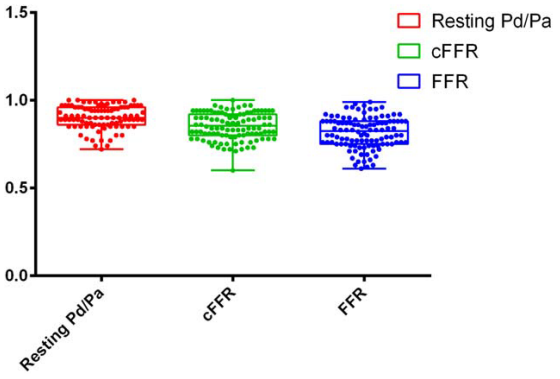

FIGURE 3 Single values and box-and-whisker plots of resting Pd/Pa, contrast medium induced Pd/Pa ratio (cFFR) and fractional flow reserve (FFR) [Color figure can be viewed at wileyonlinelibrary.com]

4.4 | Results of different hybrid decision-making revascularisation strategies

Figure 7 shows in a schematic fashion the predicted results of different hybrid decision-making revascularisation strategies. In particular:

1. A Hybrid Pd/Pa-FFR strategy would avoid adenosine use in 47% ($n = 41$) of patients evaluated (52% of stenoses; $n = 56/108$) with an associated 96.5% agreement with FFR-only strategy ($n = 83$ patients). Administration of additional contrast medium will not be required.
2. A Hybrid cFFR-FFR strategy would avoid adenosine use in 86% ($n = 74$) of patients (85% of stenoses; $n = 92/108$) with an associated 95.3% agreement with FFR-only strategy ($n = 82$ patients). This strategy will require additional injections of contrast medium in all patients.
3. The novel hybrid Pd/Pa-cFFR-FFR strategy demonstrated the best performance increasing the percentages of patients free from adenosine administration up to 90% ($n = 77$; 88% of stenoses; $n = 56/108$), avoiding additional medium contrast injection in 48% ($n = 41$) of patients (48% of stenoses; $n = 52/108$) albeit maintaining a 95.3% agreement with FFR-only strategy ($n = 82$ patients).

Possible interactions between clinical factors and FFR were explored but no confounding factors were found.

5 | DISCUSSION

We found that a simple algorithm to interrogate coronary stenoses with pressure guidewires, applicable to any available FFR system and consisting of sequential measurements of the translesional pressure ratio at baseline, contrast-induced and adenosine induced hyperemic conditions, reduces dramatically the need of hyperemic agents for physiological interrogation whilst maintaining an high classification agreement with FFR as reference. These findings could increase the adoption of a physiology-guided PCI when only conventional pressure guidewires and consoles are available.

Currently, implementation of FFR in clinical practice is still limited by some drawbacks, mainly represented by the need of adenosine administration that implies as patient's discomfort (chest pain, tachypnea, atrio-ventricular block) [10,11], work-flow time delays and additional costs, especially in case of multi-vessel disease requiring multiple FFR interrogations. To overcome these issues, other adenosine-free methodologies like iFR have recently demonstrated to be not inferior to FFR in terms of risk of MACE at one year. However, some physicians do not still have access to this technology mainly because it depend from the use of a dedicated guidewire and console. In these

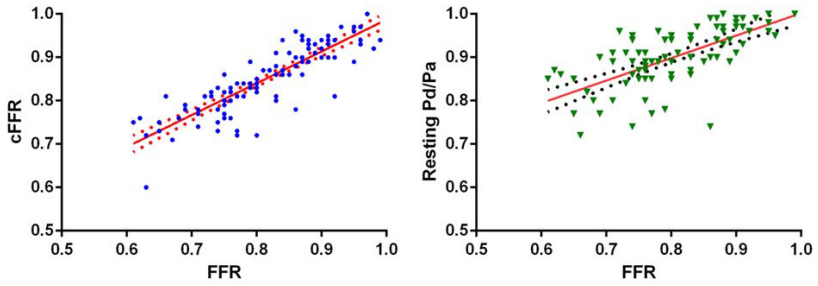

FIGURE 4 Correlation between contrast medium induced Pd/Pa ratio (cFFR) and fractional flow reserve (FFR) values (left) and Resting Pd/Pa and FFR (right) [Color figure can be viewed at wileyonlinelibrary.com]

cases, other indexes like resting Pd/Pa ratio, could be an alternative to FFR especially when combined along with FFR in an hybrid diagnostic flow-chart. Our effort, in this pivotal study, aims to create a simple and practical algorithm to interrogate the stenosis. cFFR is immediately available using conventional contrast media routinely administered for coronary angiography and does not require special software or an ECG tracing.

Thus, an hybrid Pd/Pa-FFR algorithms was proposed [8] potentially obviating the need for vasodilator drugs in more than half of patients (47%) whilst maintaining high classification agreement with an FFR-only strategy. Finally, cFFR has been reported to have a good correlation with FFR, even superior than Pd/Pa ratio [9,12] leading to further reduction in adenosine requirement when combined with FFR. Finally, the use of cFFR in clinical practice is currently under debate [13,14], therefore with our work we would provide further information on this topic.

All previous findings were confirmed by the present study as a hybrid Pd/Pa-FFR strategy would be potentially able to avoid adenosine administration in 47% of patients, whereas a cFFR-FFR strategy in 86% of them maintaining an high classification agreement (>95% for both) with FFR. Moreover, we actually expand previous finding proposing to integrate these methodologies into a novel three steps strategy (Pd/Pa-cFFR-FFR) demonstrating that the use of adenosine might be unavoidable in a very small proportion of cases (10% of patients), thus leading to a reduction in adenosine-related drawbacks as well as to an accelerated functional assessment process making the physiologic evaluation of coronary stenoses simpler and more widespread than nowadays maintaining an high classification agreement.

There are several limitations related to our study mainly represented by the observational design and the limited sample size. Given that with the contrast medium only a short period of hyperemia can be achieved, it is uncertain how to use it in case of serial stenosis. Nevertheless, we cannot provide any data regarding more complex scenario like ostial lesions or left main stenosis; at this regard most randomized control trials [1,2,6] investigating the role of FFR or IFR excluded patients with left main stenosis, thus confirming the limited experience of functional analysis in this subset. The additional need of dye related to cFFR assessment was advocated [15] as a limitation especially in patients with renal failure or in complex anatomic subsets. However, this amount is small (6 mL per stenosis) and necessary in half of

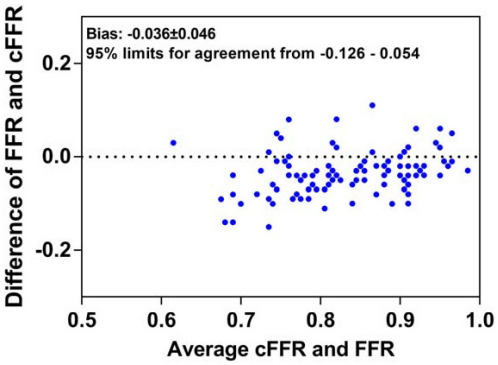

FIGURE 5 Bland-Altman plot between contrast medium induced Pd/Pa ratio (cFFR) and fractional flow reserve (FFR) across the entire range of stenoses severity [Color figure can be viewed at wileyonlinelibrary.com]

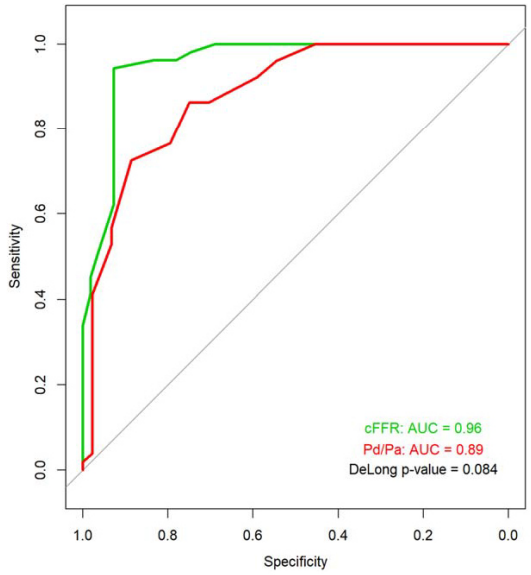

FIGURE 6 ROC curve using the threshold cut-off for fractional flow reserve (FFR) of ≤0.80. Green line = cFFR; Red line = baseline Pd/Pa [Color figure can be viewed at wileyonlinelibrary.com]

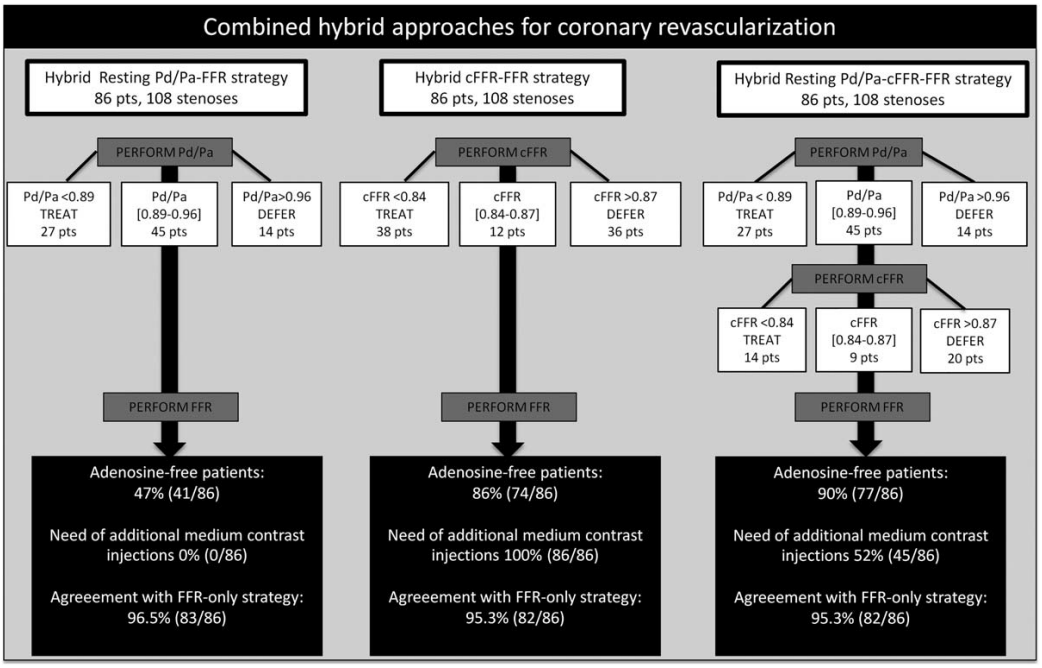

FIGURE 7 Predicted results of different hybrid decision-making revascularisation strategies

patients according to our novel multi-step approach. As a matter of fact, to limit this issue in current practice we usually perform the injection while we are ensuring the correct position of the pressure wire distal to the stenosis, without need of additional dye to complete the cFFR assessment of the target stenosis. Furthermore, as reported by Tebaldi and Colleagues [16], FFR result was significantly higher in patients with chronic kidney disease (CKD) compared to those without CKD and should be interpreted with caution in this subset. A dedicated study including patient with CKD would be required to confirm the usefulness of a combined hybrid approach also in this group. Even if in our experience the adoption of this flow-chart was easy and practical, we cannot report a step-by-step procedural time estimation that could be an important outcome for future analysis. Finally, both Pd/Pa and cFFR were compared to FFR which is a surrogate for ischemia, without been, to date, independently tested for clinical outcomes.

In conclusion, the three approaches seem to have a similar diagnostic efficiency compared with the FFR-only strategy. Overall, use of adenosine free indices, wither separately or in combination, leads to a marked reduction in the number of stenoses that require adenosine administration during physiological examination and this advantage could help in increase the current adoption of physiology assessment in clinical practice.

COMPETING INTEREST

All authors have completed the Unified Competing Interest form at www.icmje.org/coi_disclosure.pdf (available on request from the corresponding author) and declare: no support from any organization for the submitted work; no financial relationships with any organizations that might have an interest in the submitted work in the previous 3 years; no other relationships or activities that could appear to have influenced the submitted work.

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CONFLICT OF INTEREST

Dr. M. Echavarría-Pinto and Dr. J. Escaned have served as speakers in educational events organized by St. Jude Medical and Volcano Corporation. Dr. E. Cerrato has served as speaker in educational events organized by Volcano Corporation. The authors have no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from

those disclosed. The other authors have no conflict of interest to declare.

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SUPPORTING INFORMATION

Additional Supporting Information may be found online in the supporting information tab for this article.

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2.1.2. Publication No. 2, original article

"Safety of intermediate left main stenosis revascularization deferral based on fractional flow reserve and intravascular ultrasound: A systematic review and meta-regression including 908 deferred left main stenosis from 12 studies"

Cerrato E, Echavarria-Pinto M, D'Ascenzo F, Gonzalo N, Quadri G, Quirós A, de la Torre Hernández JM, Tomassini F, Barbero U, Nombela-Franco L, Nuñez-Gil I, Biondi-Zoccai G, Macaya C, Varbella F, Escaned J.

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Summary: The angiographic evaluation of LM stenosis is difficult due to its location prone to vessel foreshortening, overlapping of procimal branches and inherent difficulties in assessing ostial disease. Beyond angiography, others intravascular tool usually help the interventional cardiologist in the decision making process while assessing a coronary doubtful stenosis. such as IVUS and FFR have shown to reliably expand angiographic appraisal. However, latest European Guidelines on Myocardial Revascularization[1] recommends FFR to identify the hemodynamic relevance of coronary stenosis in stable patients when evidence of ischaemia is not else available without distinguish between LMCA or other segment) and IVUS to assess severity and optimize treatment of unprotected LMCA; with a class I, LOE: A and IIa, LOE: B, respectively. Taking together these premises, the purpose of this work was to perform a comprehensive systematic review and meta-analyses of available studies in which FFR and IVUS were used to decide upon LMCA disease, to critically appraise, separately, the long-term safety of their use for revascularization deferral. Overall, 908 LMCA stenoses from 7 FFR and 5 IVUS studies were included with median follow-up of 29.0 and 31.5 months respectively. Per year of follow-up occurrence of overall MACE were numerically similar (5.1% in FFR group and 6.4% in IVUS group) as well as death, myocardial infarction, LM revascularization. Meta-regression analysis suggested the influence of a distal LM stenosis on MACE in FFR group ($\beta = 0.06$, $p = 0.01$) and age in IVUS group ($\beta = 0.4$, $p = 0.001$). In individual studies several independent predictors of

MACE were identified including use of lower doses of intracoronary adenosine (OR 1.39, p = 0.04) in FFR group and plaque burden (OR 1.34, p = 0.025), number of other diseased vessels (OR 1.39, p = 0.04) and any untreated stenosis (OR 3.80; p = 0.037) in IVUS- studies. According to these findings, we concluded that deferring LMCA intermediate stenosis on the basis of FFR or IVUS showed an acceptable and similar risk of events in a mid-term follow-up although several different variables related to each technique showed an interaction on outcome.

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Safety of intermediate left main stenosis revascularization deferral based on fractional flow reserve and intravascular ultrasound: A systematic review and meta-regression including 908 deferred left main stenosis from 12 studies

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ABSTRACT

Background: Current guidelines recommend intravascular ultrasound (IVUS) or fractional flow reserve (FFR) to decide upon ambiguous left main (LM) disease. However, no study has compared the safety of LM revascularization deferral based on FFR or IVUS.

Methods: MEDLINE/PubMed was systematically screened for studies reporting on deferred treatment of angiographically ambiguous LM based upon FFR or IVUS evaluation. Baseline, angiographic and outcome data were appraised and pooled separately for each strategy according to random-effect models with inverse-variance weighting.

Results: A total of 908 LM stenoses from 7 FFR and 5 IVUS studies were included with median follow-up of 29.0 and 31.5 months respectively. Per year of follow-up occurrence of overall MACE were 5.1% in FFR group and 6.4% in IVUS group while death, myocardial infarction, LM revascularization were respectively 2.6%, 1.5% and 1.8% vs. 3.0%, 0.5% and 2.2%. Meta-regression analysis suggested the influence of a distal LM stenosis on MACE in FFR group ($\beta = 0.06$, $p = 0.01$) and age in IVUS group ($\beta = 0.4$, $p = 0.001$). In individual studies several independent predictors of MACE were identified including use of lower doses of intracoronary adenosine (OR 1.39, $p = 0.04$) in FFR group and plaque burden (OR 1.34, $p = 0.025$), number of other diseased vessels (OR 1.39, $p = 0.04$) and any untreated stenosis (OR 3.80; $p = 0.037$) in IVUS- studies.

Conclusions: Deferring LM intermediate stenosis on the basis of FFR or IVUS showed an acceptable and similar risk of events in a mid-term follow-up. Conversely, several different variables related to each technique showed an interaction on outcome.

1. Introduction

Adequate characterization of the stenosis located in the left main coronary artery (LM) is of critical prognostic importance. Without myocardial revascularization, a significant LM stenosis is associated with high mortality rates [1]. Conversely, revascularization of a non-significant LM stenosis implies patient exposure to unnecessary risks and increased costs [2].

Abbreviations: IVUS, intravascular ultrasound; FFR, fractional flow reserve; LM, left main coronary artery; MACE, major adverse cardiac events; MLA, minimum lumen area; MLD, minimum lumen diameter; PCI, percutaneous coronary intervention; LAD, left anterior descending; LCX, left circumflex.

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The angiographic evaluation of LM stenosis is difficult due to its location prone to vessel foreshortening, overlapping of Left Anterior Descending (LAD)/Left Circumflex (LCX) branches and inherent difficulties in assessing ostial disease. To overcome these limitations, adjunctive diagnostic tools, such as intravascular ultrasound (IVUS) and fractional flow reserve (FFR) have shown to reliably expand angiographic appraisal. The last Expert Consensus Statement of the Society of Cardiovascular Angiography and Interventions (*SCAI*) [3] indicated as reasonable the use of both FFR (class IIa, level of evidence (LOE): A) and IVUS (class IIa, LOE: B) to define the severity of LM intermediate stenosis, and the 2014 European Guidelines on Myocardial Revascularization recommends FFR to identify the hemodynamic relevance of coronary stenosis in stable patients when evidence of ischaemia is not else available (including LM) and IVUS to assess severity and optimize treatment of unprotected LM; with a class I, LOE: A and IIa, LOE: B, respectively [2]. Very importantly, both European and *SCAI* guidelines state that, since no high-quality study has sought to compare the safety of LM revascularization deferral based on FFR or IVUS, it is currently unclear which intravascular technique should be preferred for LM assessment.

The purpose of our work was to perform a comprehensive systematic review and meta-analyses of available studies in which FFR and IVUS were used to decide upon LM disease, to critically appraise, separately, the long-term safety of their use for revascularization deferral.

2. Methods

The present research was elaborated according to current guidelines, including the Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) amendment and recommendations from The Cochrane Collaboration and Meta-analysis Of Observational Studies in Epidemiology (MOOSE) [4,5].

2.1. Search strategy and study selection

Pertinent articles were searched in Medline, Cochrane Library, Biomed Central and Google Scholar in keeping with established methods [6]. Mesh strategy included terms related to the assessment of ambiguous LM, use of FFR or IVUS: ((fractional AND flow AND reserve) OR (FFR) OR (pressure AND wire) OR pressure wire) OR ((IVUS) OR (Intravascular AND ultrasound) OR (ultrasound)) AND (left AND (stem OR main) OR (left main)) AND ((myocardial AND infarction) OR (revascularization OR bypass OR angioplasty) OR (death)) NOT (review[pt] OR editorial[pt] OR letter[pt]). English language restriction was applied. Search strategy and protocol were published and available on web [7]. Two independent reviewers (E.C. M.EP) first screened retrieved citations at the title and/or abstract level, with divergences resolved after consensus. If potentially pertinent, they were then appraised as complete reports according to the following inclusion criteria: (i) intermediate/ambiguous LM stenosis, (ii) FFR or IVUS measurement, (iii) revascularization deferral decision based on these techniques, and (iv) long-term outcomes reported as death, myocardial infarction (MI), and LM revascularization. Exclusion criteria were (i) duplicate reporting (in which case the manuscript reporting the largest sample of patients was selected); (ii) studies reporting only single case reports, (iii) studies without reported follow-up and (v) not reporting outcomes of interest. From pertinent studies, only data about patients in which revascularization was deferred on the grounds of FFR or IVUS were included.

2.2. Data extraction

Two unblinded independent reviewers (E.C, F.DA) abstracted the following data on pre-specified forms: authors, journal, and year of publication, location of the study group, baseline features, angiographic features, FFR and IVUS features and clinical presentation. End-points of interest were death, myocardial infarction (MI) related to LM, LM revascularization and the composite of these three defined as MACE (major adverse cardiac events).

2.3. Internal validity and quality appraisal

Unblinded independent reviewers (E.C F.DA) evaluated quality of included studies on pre-specified forms. Modifying the MOOSE items to take into account the specific features of included studies, we separately abstracted and appraised study design, setting, data source, statistical methods as well as risks of analytical, selection, adjudication, detection, and attrition bias (expressed as low, moderate, or high risk of bias, as well as unclear, where it was not possible to ascertain the underlying risk of bias). For the quality assessment of the selected studies we used the Newcastle-Ottawa Scale (NOS) for Assessing the Quality of Nonrandomized Studies in Meta-Analysis [8].

2.4. Data analysis and synthesis

Continuous variables are reported as median and quartiles 1 and 3 (Q1–3). Categorical variables are expressed as n/N (%). Statistical pooling was performed with random-effect models with generic inverse-variance weighting, computing risk estimates with its 95% confidence intervals. Overall and subgroup analysis was performed in IVUS studies group that was divided into three groups: i) IVUS, MLA cut-off 6 mm^2; ii) IVUS MLA cut-off 7.5 mm^2 and iii) IVUS, operator's decision. Small study bias was appraised by graphical inspection of funnel plots. Standard hypothesis testing was set at the two-tailed 0.05 level. Independent predictors of MACE at multivariate analyses were investigated in each study separately and reported as Hazard Ratio (HR) with its 95% confidence intervals (CI). HRs from studies reporting the same predictor were pooled together according to a random-effect model with generic inverse-variance weighting, computing risk estimates with 95%. Pooled analyses were made using RevMan 5 (The Cochrane Collaboration, The Nordic Cochrane Centre, Copenhagen, Denmark). Metaregression analyses were performed for baseline and periprocedural features to assess the effect on MACE at follow-up using Comprehensive Meta-Analysis software (Biostat Software, New York, USA). Publication bias was assessed by graphical inspection of funnel plots and Egger's test.

3. Results

A total of 94 citations were firstly screened and appraised at abstract level. From these, 25 articles were selected, from which 13 were discarded because they did not meet our selection criteria [9–21]. Finally, seven studies with FFR [22–28] and five with IVUS [29–33] were included in our review (Fig. A, Supplement material).

3.1. General characteristics of studies included in this systematic review

The methodological and quality assessment is reported in Supplemental Fig. B. Overall, studies were of average quality. All were performed in Europe or North America, with a prospective and single-centre design, with acceptable risk of analyzed bias. For each study, deferral thresholds for FFR and IVUS were recalled (Table 1). In most studies, patient status was recorded at outpatient clinic examination or by telephone interview. Detailed information about outcomes and follow-up definition is reported in data supplement, Table A. In all studies follow-up angiography was performed only in case of recurrent complaints. FFR cut-off was 0.75 in four of seven studies and 0.80 in the other three. Five out of seven studies used intravenous administration of adenosine (140 μg/kg per min for >2 min) through a femoral vein. Three IVUS studies [28–30] pre-specified the minimum lumen area cut-off to defer the treatment (6 mm^2 in two studies, 7.5 mm^2 in one) whilst in the remaining two the decision was taken by the operator. In these 2 studies, mean MLA in the deferred group was 10.4 mm^2 [33] and 9.3 mm^2 [29]. Notably, almost all FFR studies excluded patients with acute coronary syndrome at presentation, whilst 4 of 5 IVUS studies allowed unstable patients (ranging from 20% to 64% of cases) but excluding complicated LM (ulceration, dissection, or thrombus) in most.

3.2. General characteristics of patients in whom LM revascularization was deferred based on FFR and IVUS

A total of 908 LM stenoses in which revascularization was deferred on the grounds of FFR (345 patients) or IVUS (563 patients) were included in the quantitative analysis. Baseline and peri-procedural characteristics are reported in Table 2 and Table B Supplement Material. Median age was similar between FFR (63.8 years [60.8–64.8]) and IVUS (63.4 [63.0–64.5]) studies, and most patients were male (76.5 (75.0–79.5) and 67.0 (62.0–86.6) respectively in FFR and IVUS studies). Prevalence of diabetes was similar (median 22.5% [20.0–25.8] vs. 24.5% [22.5–28.5] in FFR and IVUS studies, respectively) while smoking was more prevalent in FFR studies (median 44.0% [32.5–48.8] vs 24.0% [21.2–24.6] in IVUS group). Notably, the angiographic characteristics of the included LM stenoses were similar between both groups (diameter of stenosis = 45.0% [37.2–44.8] in IVUS vs. 42.5% [44.1–46.5] in FFR studies) as well as distal LM involvement (51.0% [50.0–66.0]) vs. 51.0%

Table 1
Information about selected studies with FFR/IVUS deferred strategy. STEMI: ST-elevation myocardial Infarction; VD: Vessel Disease; AMI: Acute myocardial Infarction; CCS Canadian Cardiovascular Society grading scale for angina; LAD: Left Anterior Descending; LCA: Left Coronary Artery.

First author, year of publication	Journal	Deferred lesions included ($n = 345$)	Design/region	FFR cut-off or IVUS area cut-off	Adenosine administration	Clinical presentation	Follow-up duration (months ± SD)
FFR studies							
Bech, 2001	Haart	24	Prospective, two centers/Europe	0.75	Femoral vein, infusion rate of 140 μg/kg per min for 2–4 min.	All-comers to angiography	29 ± 15
Courtis, 2009	Am J Cardiol	82	Prospective, single center/North America	<0.75 and >0.80 (additional clinical data if FFR was between 0.75 and 0.80)	Intracoronary administration of adenosine at a dose ≥30 μg	All-comers excluding: STEMI within 24 h and other VD	14 ± 12
Hamilos, 2009	Circulation	138	Prospective single center/Europe	0.8	Femoral vein, infusion rate of 140 μg/kg per min for >2 min.	Stable CCS I-IV	35 ± 25
Jasti, 2004	Circulation	37	Prospective, single center/North America	0.75	Intracoronary infusion of adenosine (42 to 56 μg),	Allcomers excluding: Recent AMI, 3VD, unstable angina	38
Jimenez-Navarro, 2004	Invasive Cardiology	20	Prospective, single center/Europe	0.75	Femoral vein, infusion rate of 140 μg/kg per min for more during 2 min.	All-comers excluding: AMI within 4 days, cardiogenic shock, 3VD	26 ± 12
Legutko, 2005	Kardiol Pol	20	Prospective, single center/Europe	0.75	Femoral vein, infusion rate of 140 μg/kg per min over 5 min	Stable setting excluding: other severe VD in LCA.	24
Lindstaedt, 2006	Am Heart J	24	Prospective, single center/Europe	<0.75 and >0.80 (additional clinical data if FFR was between 0.75 and 0.80)	Femoral vein, infusion rate of 140 μg/kg per min for more during 1.5 min.	All-comers excluding: AMI within 10 days, Severe VD both in LAD and Cx.	29 ± 14
IVUS studies							
De La Torre Hernandez (LITRO), 2011	JACC	179	Multicenter, prospective/Europe	6	–	All-comers to angiography (47% ACS, excluding LM ulceration, dissection or thrombus or LM as culprit lesion)	24
De la Torre Hernandez, 2007	Rev Esp Cardiol	48	Single-center, prospective/Europe	6	–	All-comers to angiography (64% ACS, excluding ulceration, dissection, or thrombus or LM as culprit lesion)	40 ± 17
Fassa, 2005	JACC	114	Retrospective/ North America	7.5	–	All-comers to angiography (10.5% UA; 8.8% AMI)	43.2
Okabe, 2008	J. invasive cardiol	100	Single center, prospective (only deferred lesion)/ North America	Clinicians decision	–	All-comers to angiography	31.5 ± 17
Abizaid, 1999	JACC	122	Single center, prospective/ North America	Clinicians decision	–	All-comers to angiography (46% UA)	11.7

[34.8–56.3] respectively). Concomitant presence of at least another vessel with stenosis (>50%) was reported in about 60% of cases in both IVUS and FFR studies.

Table 2
Baselines, angiographic and peri-procedural features. CAD: coronary artery disease; MLD: minimum lumen diameter; MLA: minimum lumen area; LM: left main coronary artery.

	LM lesion FFR-deferred ($n = 343$, 7 studies)	LM lesion IVUS-deferred ($n = 563$, 5 studies)
Age (years)	63.8 (60.8–64.8)	63.4 (63.0–64.5)
Male gender	76.5 (75.0–79.5)	67.0 (62.0–86.6)
Hypertension	42.5 (33.7–51.5)	58.0 (50.9–60.0)
Smoker (former or current)	44.0 (32.5–48.8)	24.0 (21.2–24.6)
Diabetes mellitus	22.5 (20.0–25.8)	24.5 (22.5–28.5)
Dyslipidemia	53.9 (37.7–69.5)	48.3 (48.0–65.9)
Familiarity for CAD	17.0 (13.0–28.5)	30.8 (22.4–39.2)
Ejection fraction (%)	58.9 (58.2–59.8)	53.0 (50.0–56.6)
MLD (mm)	2.24 (2.23–2.28)	1.92 (1.83–1.88)
Stenosis (%)	42.0 (36.4–43.5)	45.0 (44.1–46.5)
IVUS MLA	–	9.3 (9.3–10.4)
FFR	0.88 (0.87–0.90)	–
Distal LM stenosis	51.0 (50.0–66.0)	51.0 (34.8–56.3)
Other than LM diseased vessels:		
1 vessel disease	38.0 (32.0–41.0)	37.0 (35.5–52.1)
2 vessels disease	24.0 (22.8–28.1)	24.0 (18.0–37.0)
3 vessels disease	0 (0–8)	0 (0—11)

Values are median of numbers or median of percentages with 25th and 75th percentiles.

3.3. Safety of LM revascularization deferral based on FFR and IVUS

Overall, median follow-up was 30.3 months, slightly shorter in FFR studies (29.0 months [Q1–3: 25.1–32.0]) as compared to IVUS studies (31.5 months [Q1–3: 24.0 40.8]). The per year of follow-up occurrence of overall MACE was 5.1% [1.9–8.2] in FFR group and 6.4% [3.1–9.7; all 95% confidence intervals] in IVUS group (Fig. 1). In IVUS subgroup analysis, MACE occurrence was 5.7% (2.69–8.73) deferring with MLA cut-off <6 mm^2; 5.6% (2.21, 8.95) deferring with MLA cut-off <7.5 mm^2 while 8.8% (−3.06, 20.61) in operator's decision subgroup (Fig. 2). Death, myocardial infarction and LM revascularization were respectively 2.6% [0.7–4.5], 1.5% [−1.2–4.1], 1.8% [0.4–3.2] in the FFR group and 3.0% [1.6–4.4], 0.5% [−0.6–1.6] and 2.2% [0.2–4.2] in the IVUS group] (Figs. C, D and E of supplement material). The crude event rate is reported in Table C, supplement material). Meta-regression analysis suggested the influence of distal LM stenosis on MACE in FFR group ($\beta = 0.06$ [0.01–0.11] $p = 0.01$) and of age in IVUS group ($\beta = 0.4$ (0.15–0.66) $p = 0.001$). No other cofactors influenced the outcomes (Table D, supplement material). Multiple regression analysis in individual FFR studies identified as independent predictors of MACE diabetes type 2 (HR 4.40, 95% CI 1.17–16.42; $p = 0.023$) and the use of lower doses of intracoronary adenosine (HR 1.39 [1.02–1.89]; 95% CI, $p = 0.041$) while in IVUS studies, plaque burden at the MLA site (HR 1.34, 95% CI 1.03–1.73; $p = 0.025$), number of other vessels diseased excluding LM (HR 1.39 95% CI 1.01–1.90 $p = 0.044$), age (HR 1.05 95% CI

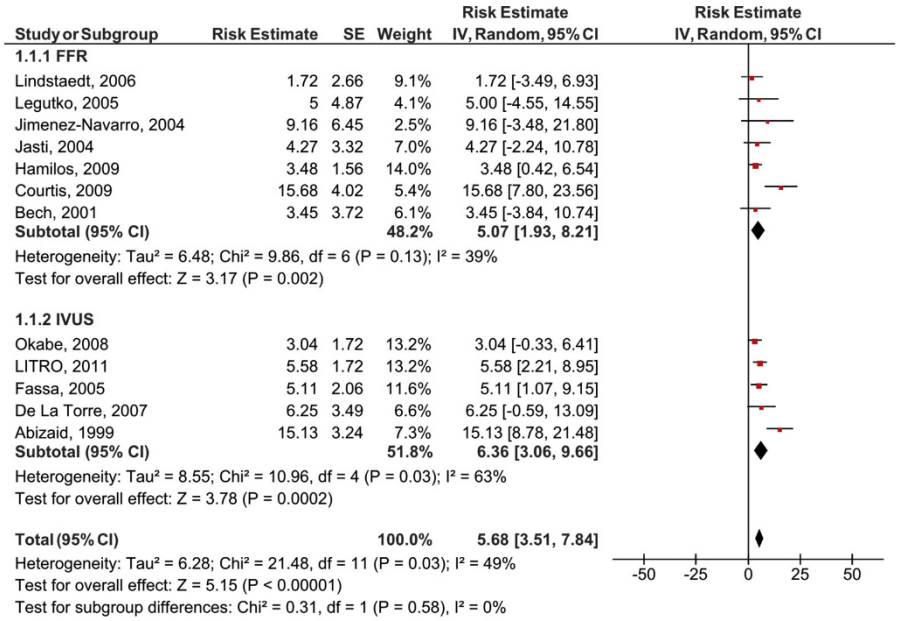

Fig. 1. Pooling of per year follow-up occurrence of overall MACEs in FFR and IVUS deferred LM studies.

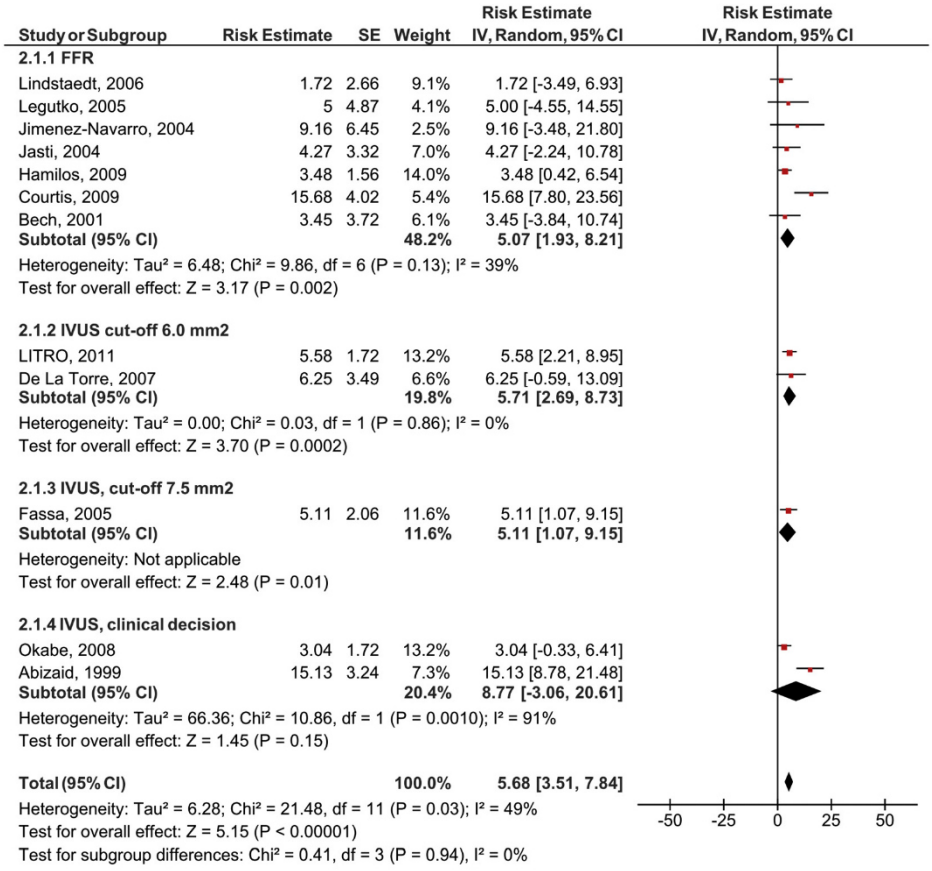

Fig. 2. Pooling of per year follow-up occurrence of overall MACEs in FFR and IVUS deferred LM studies including subanalysis according to IVUS utilization in the decision-making process.

1.02–1.09 $P = 0.004$), smoking habit (HR 2.42 95% CI 1.13–5.14 $p = 0.022$), any untreated vessel with a stenosis >50% (HR 3.80; 95% CI 1.08–13.34 $p = 0.037$) and diabetes type 2 (HR 6.32, 95% CI 1.82–22.04; $p = 0.004$) were independent predictors of MACE (Fig. F, Supplement material). At funnel plot analysis, low selection bias was noted (Data supplement, Fig. G, supplement material); Egger's test was not significant ($p = 0.78$).

4. Discussion

In this work, we performed a systematic review on the safety of LM stenosis deferral based on IVUS or FFR. Our main finding is that the safety of LM revascularization deferral based on IVUS or FFR seems to be associated with a similar risk of MACE at medium term. Moreover, several different variables related to each technique showed an association with outcome. Findings, however, are limited by the fact that no direct data allows a full statistical comparison between the two techniques. Still, this work constitutes the first objective and quantitative comparison between the two available adjunctive invasive diagnostic tools recommended in clinical guidelines for ambiguous LM assessment [2,3].The advantages and limitations of FFR and IVUS for LM assessment and the implications of our observations will be discussed next.

4.1. Advantages and limitations of ambiguous LM disease deferral based on FFR

FFR theoretical framework requires maximal hyperaemia. This can be hampered by inadequate administration of adenosine, particularly in ostial LM stenosis, if intracoronary route is chosen. As a matter of fact, one of the studies [23] identified low dosage of intracoronary adenosine as a determinant of long-term events, suggesting the possibility of false negative results. This might constitute a warning for operators and an argument against the use of intracoronary adenosine especially in the setting of ostial LM lesions and supporting a wider use of intravenous administration of adenosine for LM stenosis interrogation, because it allows enough time to disengage the guiding catheter and for a pullback maneuver. Additionally, another potential source of error is the engagement of the stenosis in the diseased LM as a consequence of suction caused by increased hyperaemic flow. Among FFR included studies ostial LM involvement was reported in a percentage ranging from 28% to 45% (see Supplemental Table B). However, besides the recommendation to avoid intracoronary adenosine in case of ostial involvement, we cannot estimate in how many cases it was used in this specific setting in our population.

Interestingly, distal LM stenosis showed a significant interaction for MACE in FFR studies, such that its presence was associated with a worse outcome. It is of note that four out of seven FFR studies [20,22–24] included patients with Left Anterior Descending (LAD) and/or Left Circumflex (LCX) stenoses, reflecting real life in clinical practice. Interestingly, distal LM disease more commonly coexists with stenoses in the proximal LAD and LCX, and theoretically, FFR across an intermediate LM stenosis might be affected by the presence of severe downstream disease, even if the pressure wire is positioned in the non-diseased downstream vessel [34]. Therefore, it can be hypothesized that the interaction between distal LM and MACE in FFR studies could be partly due to the limitations of FFR assessment when severe distal disease is present. However, data from the Stanford group [34] tested this hypothesis showing that distal disease only affects LM FFR in the presence of downstream severe epicardial disease suggesting to use IVUS in such cases when FFR measurement range from 0.80 to 0.85. Overall, it is unlikely that concomitant downstream disease could substantially affect LM FFR in the majority of cases. From a pragmatical point of view, and to avoid any risk of bias, it will be advisable to confirm the pressure gradient across the LM by measuring FFR in both the LAD and LCX and by always performing a pullback maneuver during i.v. adenosine infusion. Notably, the implementation of this maneuver was not clearly defined in the selected studies and although many operators usually feel more reassured by using IVUS for distal LM assessment, the prevalence of distal disease to the LM was similar in the FFR and IVUS study groups. Finally, although any inference is limited by the small sample size, when we repeated analysis excluding FFR studies in which adenosine was administered as an intracoronary bolus [23,25], the per year of follow-up occurrence of overall MACE decreased to 3.4% [1.0–5.7, Fig. H, Supplemental material).

An inherent limitation of the present analysis is that the IVUS and FFR criteria used for LM stenosis deferral varied between some studies. It might be argued that the use of a 0.80 FFR cut-off might lead to a safer identification of non-significant LM stenosis (higher negative predictive value than the 0.75 FFR cut-off). However, and as a matter of fact, the event rate was not substantially different when pooling separately those studies [22,25–27] that used 0.75 as FFR cut-off. (4.7% [95% C.I. 0.6–8.7] for MACE as compared to the overall group (5.1% [1.9–8.2]).

4.2. Advantages and limitations of ambiguous LM disease deferral based on IVUS

At a difference from other locations in the coronary tree, the amount of myocardium subtending the LM is relatively stable. Hence, a single MLA IVUS cut-off might work better in this location as compared to its use in more distal branches, where the correlation between the anatomical stenosis severity, as assessed by IVUS, and the functional significance of the stenosis, as assessed by FFR, is only modest, because the trans-stenotic flow depends on the viability and extension of the downstream myocardial bed, among other factors. Additionally, IVUS interrogation allows the quantification of atheromatous plaque burden. It is important to remember that long-term outcome in patients with coronary atherosclerosis is influenced by both ischemic burden and extent of atherosclerotic disease [35,36]. As a matter of fact, in one of the studies included in this analysis, IVUS-derived plaque burden at the LM stenosis was identified as a predictor of events in the long term. Additionally, we observed that the presence of untreated vessel and diabetes type 2 [29] were independent predictors of MACE. Of note, in this case MACE were largely driven by subsequent revascularization procedures undertaken at the discretion of the interventionist.

In our review, besides the study from Fassa [32] with 7.5 mm^2 as cut-off for deferral, we included also two studies [29,33] in which decision of deferral after IVUS examination was left to the operator's discretion. To overcome this limitation of the present analysis while keeping the largest amount of available data, we also reported the analysis according to event occurrence in each group, separately. Interestingly, we found no substantial differences in terms of MACE occurrence including only the two studies [30,31] with IVUS cut-off <6 mm^2 (5.7% [2.69–8.73] or in case of IVUS cut-off <7.5 mm^2 (5.1% [1.07–9.15]) while the risk of events seems numerically higher when deferral was left to the operator's decision (8.8% [−3.06–20.61]). Even if this finding is limited by the low sample size, it reassures the importance of cut-off utilization as suggested by recent studies.

Previous studies tried to offer a conjunctive analysis of the relationship between anatomy of a diseased LM and physiology [37]. Park et al. [18].investigated 112 patients with isolated LM stenoses (30% to 80% diameter stenosis severity) that underwent both IVUS and FFR before revascularization. LM MLA recorded by IVUS was an independent predictor of an FFR >0.80 (adjusted OR: 0.37, $p < 0.001$) and the optimal IVUS MLA cut-off for an FFR of ≤0.80 was 4.5 mm^2 (77% sensitivity, 82% specificity). Similarly, lesion length on angiography was also found to be significantly in relation with FFR [17]. As such, the dynamic relationship between lesion length, MLA (by IVUS), and FFR remains still under investigation. Following this argument, it is likely that longer, diffuse lesions with larger IVUS-derived MLA might be ultimately found to harbour greater physiological significance than short, focal lesions with lesser MLAs. Still however, the ongoing evidence supporting the use of IVUS-derived MLA seems to support the safety of LM

revascularization deferral based on a single MLA cut-off. The clinical implication of this relationship is still uncertain but suggests again a combined anatomical and physiological approach to provide a more extensive evaluation of an intermediate LM stenosis. Nevertheless, LM-MLA cut-off value seems to be population dependent and ethnicity related as we can suspect looking how different is the average LM-MLA in the study of Fassa [32] performed in North America (7.6 mm^2), compared to the study from Park [18] performed in Korea (4.8 mm^2). However, in the latter the sensitivity (77%) and negative predictive value (75%) for a 4.5 mm^2 were clearly subottimal, thus advocating extreme caution in cut-off value definition [38]. In our opinion, a 6 mm^2 cut-off value, which is clinically validated in a prospective trial [30] and nicely derived by linear law [39,40] (assuming 3 mm^2 as the best cut-off MLA value for LM branches) should be preferred to allow a safe deferral. In order to overcome the limitations related to each technique, a recent algorithm [38] was proposed suggesting a two-step approach recommending FFR use in case of MLA value too close to the cut-off value (between 5 and 6 mm^2).

4.3. Limitations

Our study has several limitations. Firstly, we are attempting to compare two different techniques and since FFR and IVUS are distinct by nature, a direct comparison does not seem feasible. To overcome these limitations we pooled separately data testing the safety of deferral based on one or other technique. The heterogeneity of the studies in terms of population, deferral criteria and patient's and procedural features represents a source of bias, which might also limit the applicability of our findings. Because of the amount of missing data a statistical analysis investigating the relationship between specific clinical or angiographic features and outcome in overall studies is not feasible. Finally studies do not provide information regarding medical regimen including dual antiplatelet therapy, beta blockers or statin use in this high-risk deferred population.

Still, this work constitutes the first objective and quantitative comparison between the two available adjunctive invasive diagnostic tools recommended in clinical guidelines for ambiguous LM assessment and up to date we do not have definitive data coming from randomised trials.

5. Conclusions

Deferring LM intermediate stenosis on the basis of FFR or IVUS showed an acceptable and similar risk of events in a mid-term follow-up. Several different variables related to each technique showed an interaction on outcome and have to be kept in mind when approaching the evaluation of an ambiguous LM.

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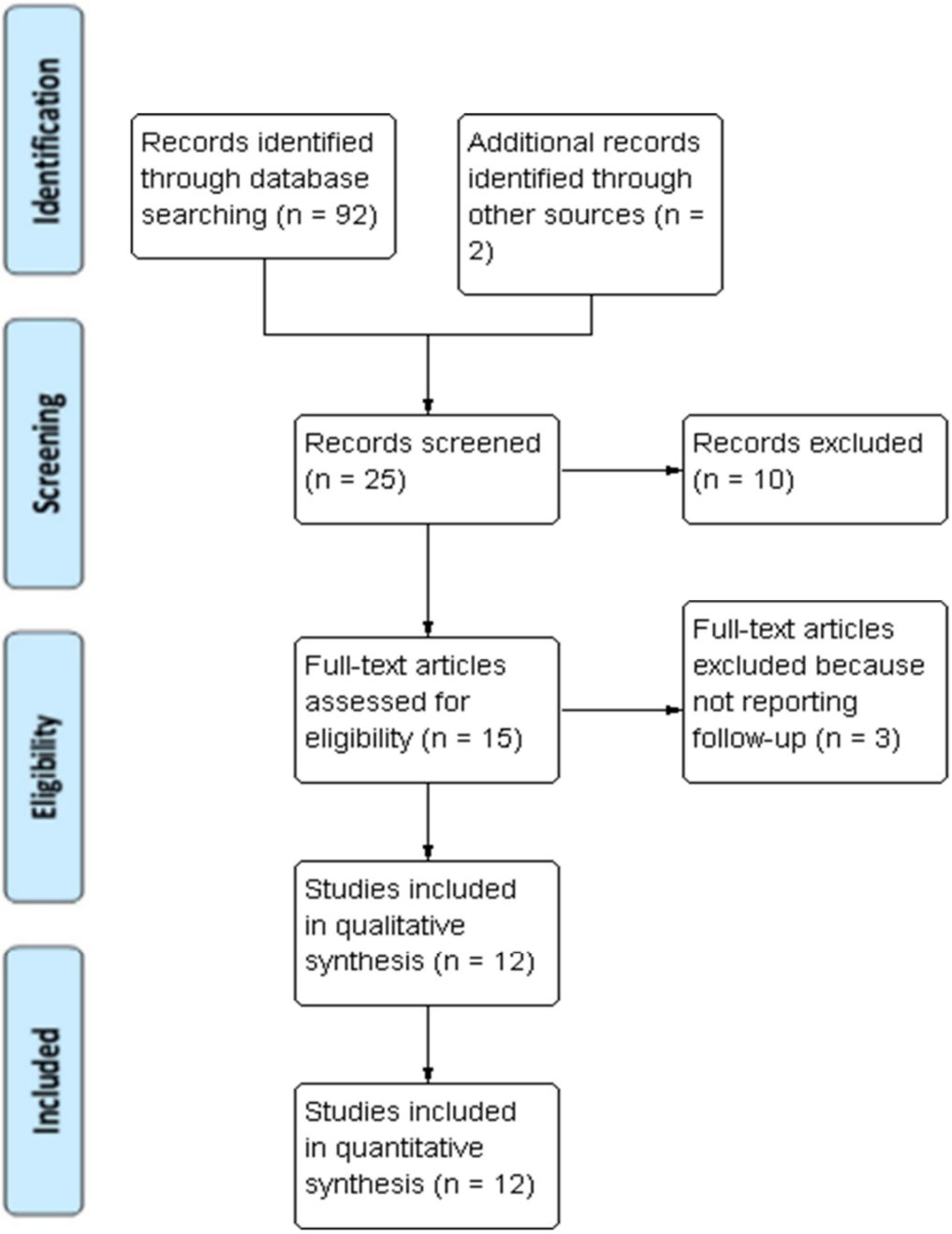

Figure. A - review profile

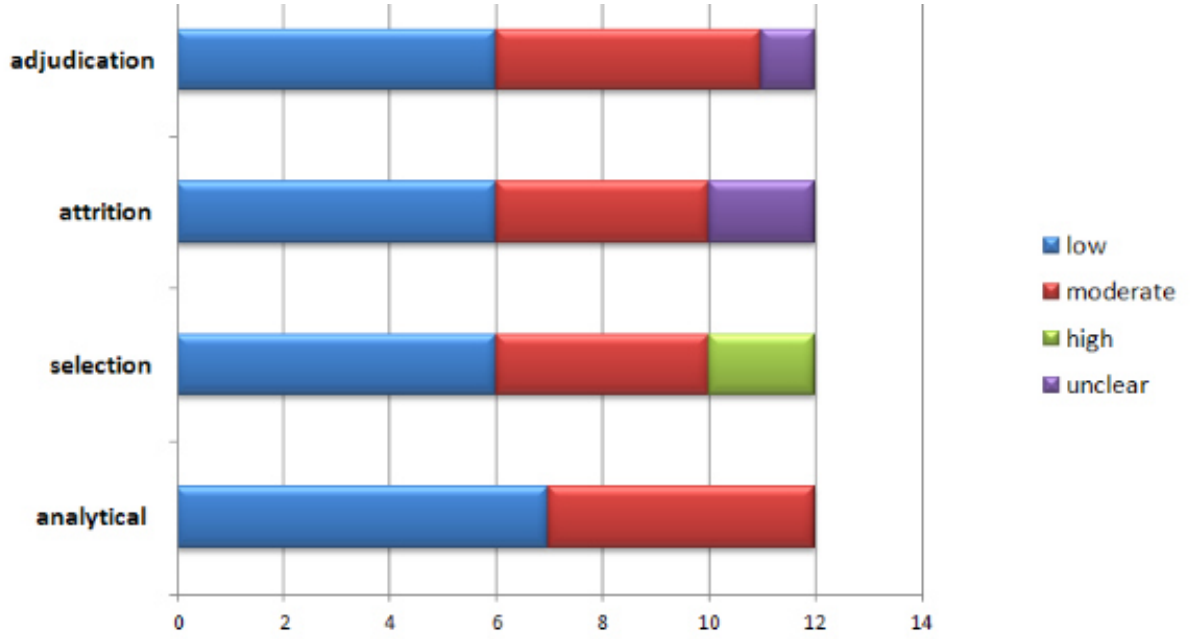

Figure B – Bias

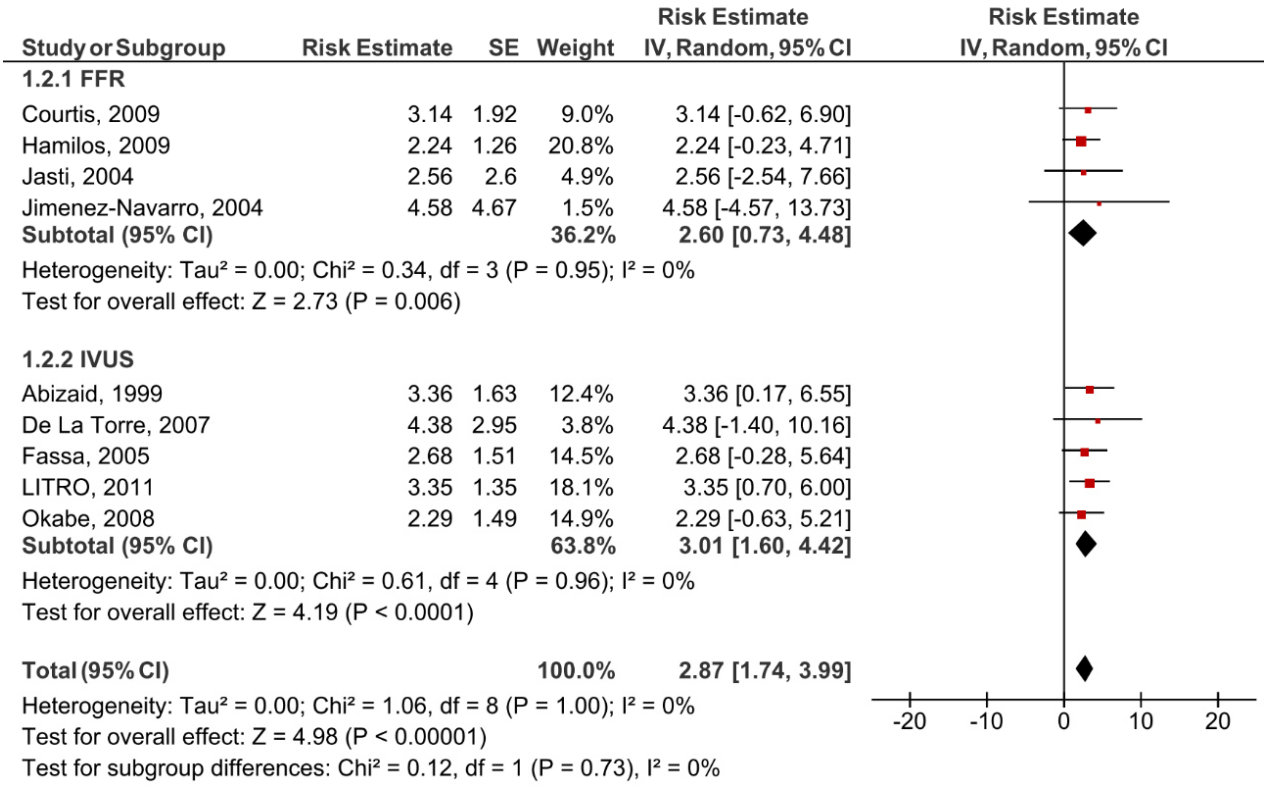

Fig. C – Overall risk estimate for Death

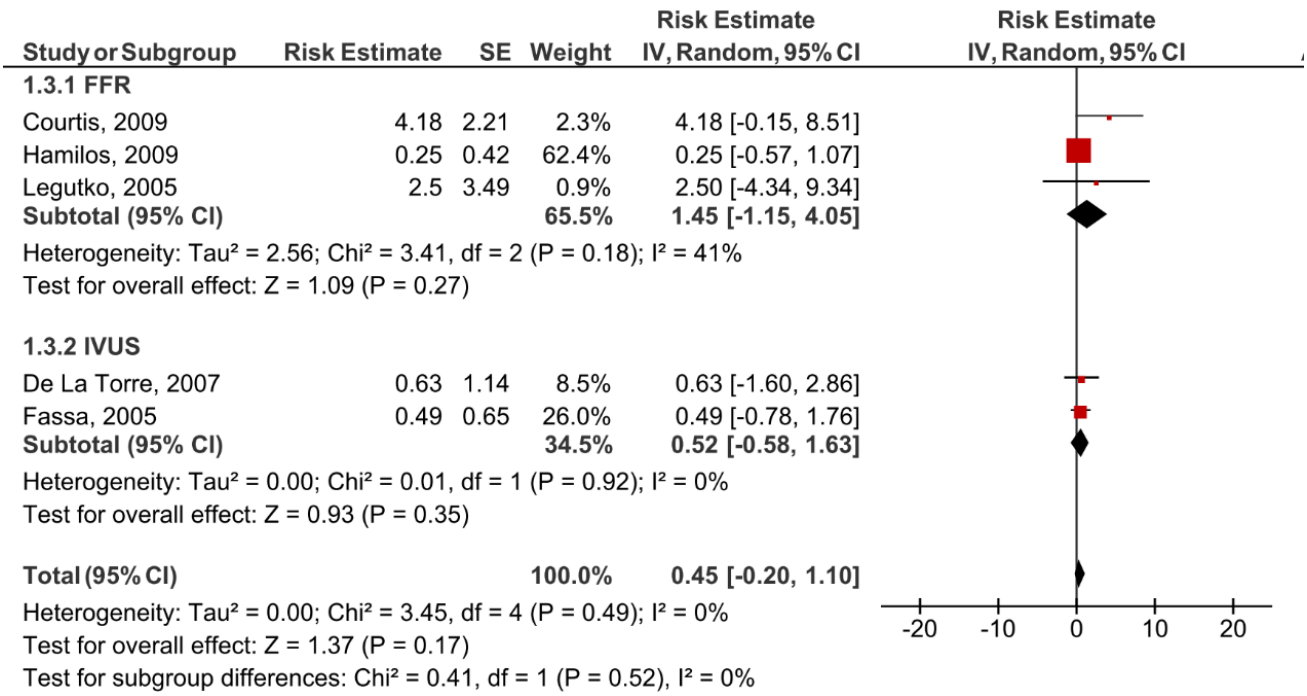

Fig. D - Overall risk estimate for MI

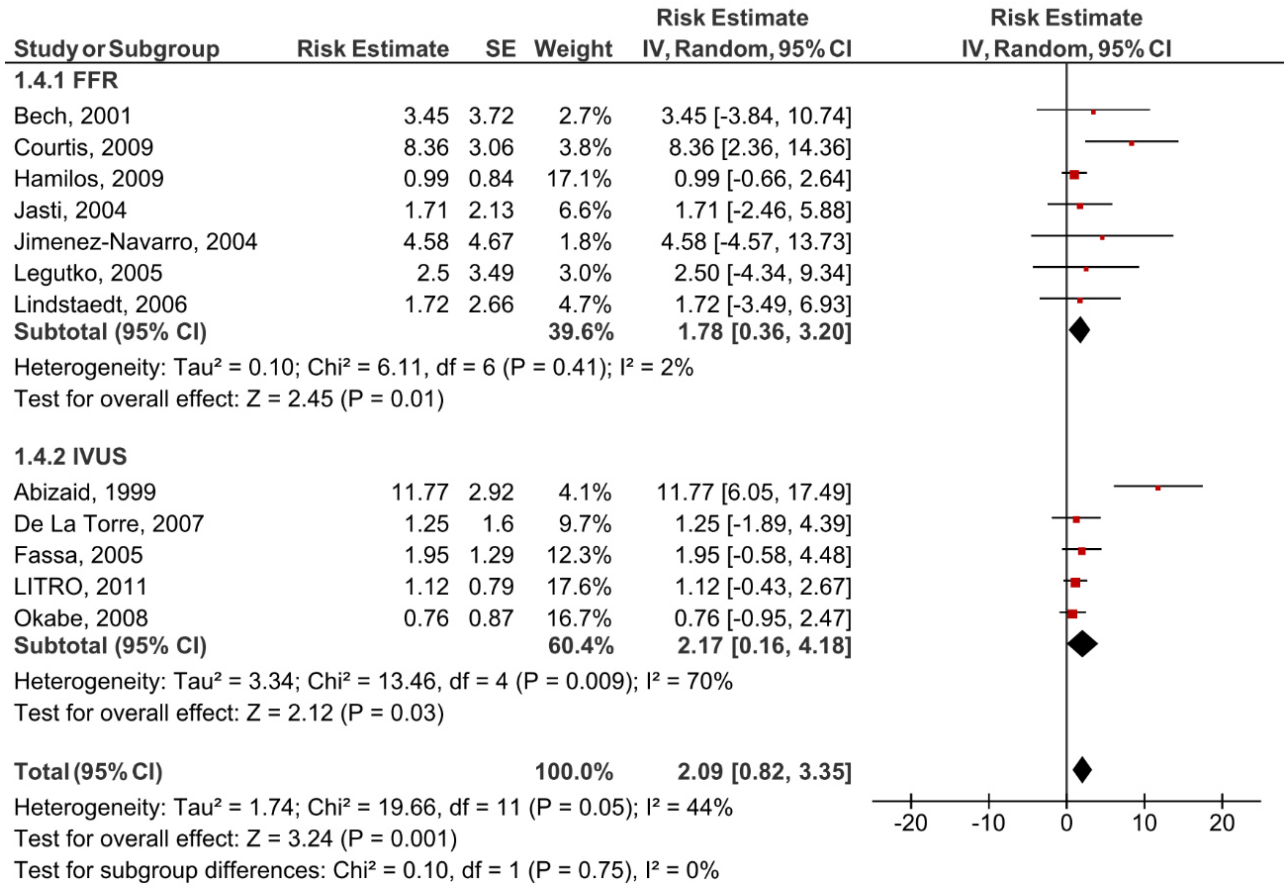

Fig. E - Overall risk estimate for TLR

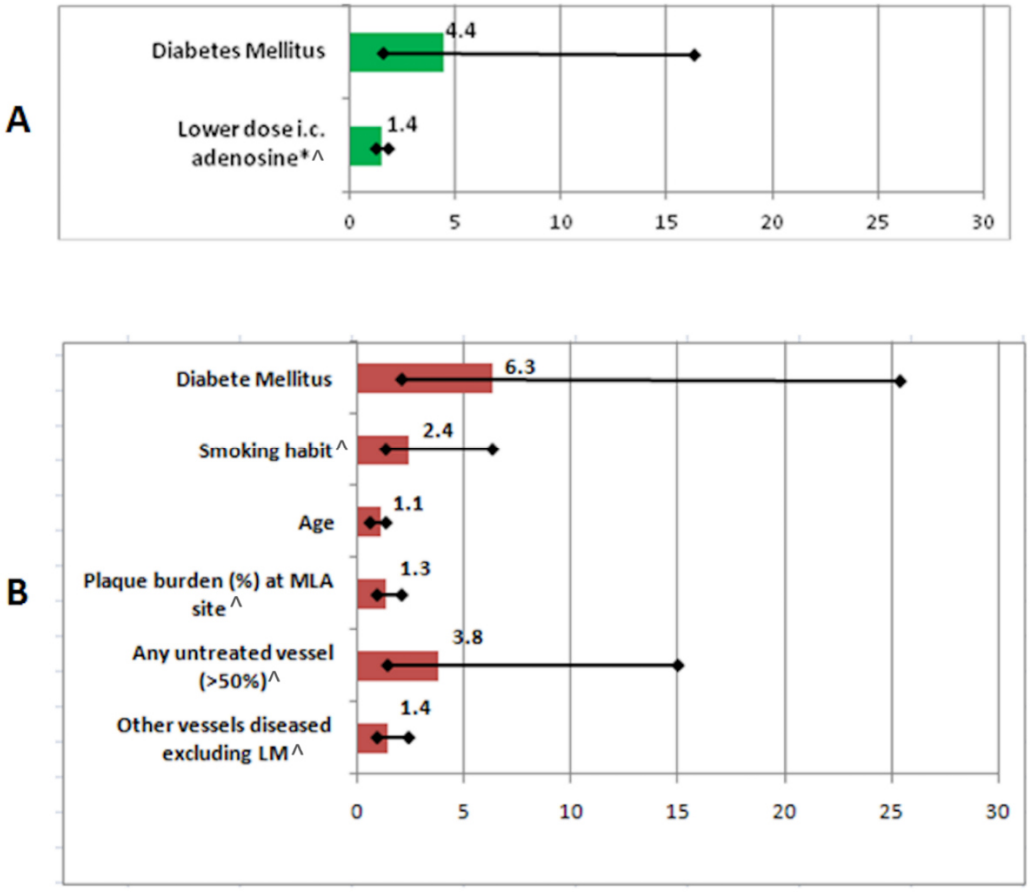

Fig. F – Predictors of MACE in case of FFR deferral (panel A) or IVUS deferral (panel B)

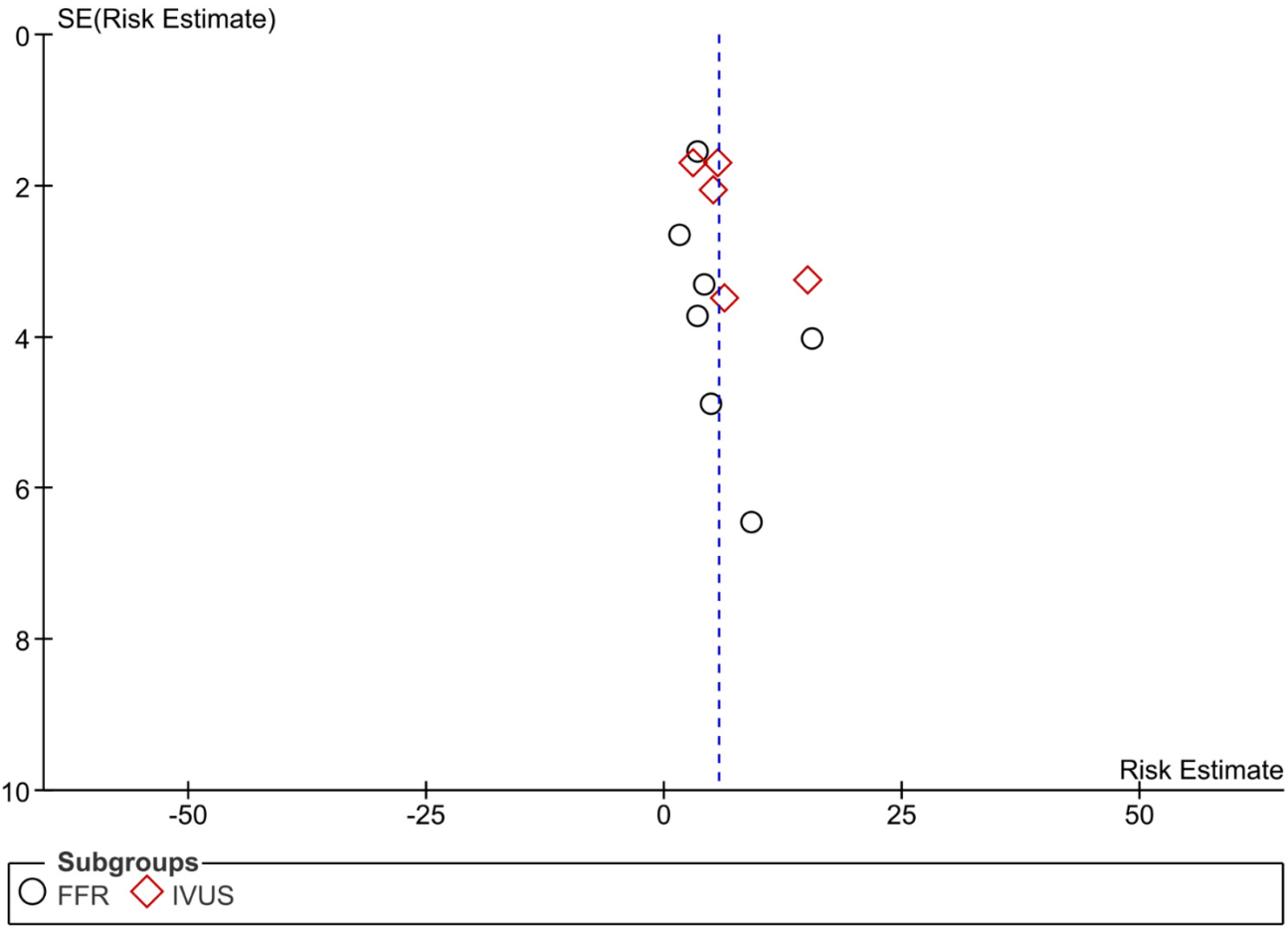

Fig. G - Funnel plot

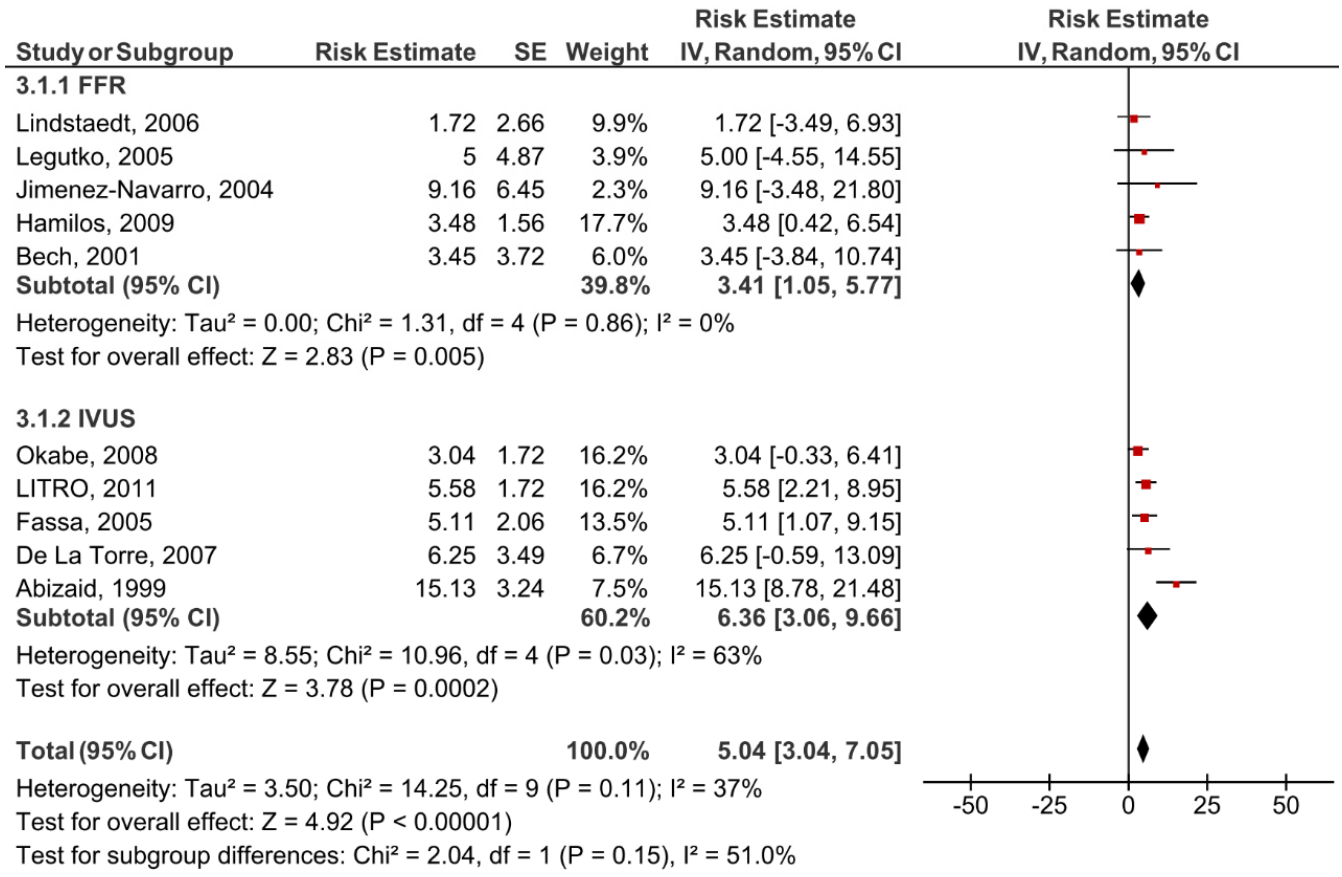

Fig. H – Overall risk estimate for MACE, including only studies with FFR performed with intravenous administration of adenosine.

First Author, year of publication	Modality	Study Outcomes	Follow-up modality	Completeness of Follow-up (%)
Bech, 2001	FFR	Death, MI, any revascularization, LM revascularization	Clinical visits at least once a year. Angiographic follow in case of recurrent complaints or coronary events.	100
Courtis, 2009	FFR	Death, MI, any revascularization, LM revascularization	Clinical visits and/or phone contact.	100
Hamilos, 2009	FFR	Death, MI, any revascularization, LM revascularization	Clinical visits. Angiographic follow in case of recurrent complaints or coronary events.	98
Jasti, 2004	FFR	Death, MI, any revascularization, LM revascularization	Serial telephone interview every 6 months and office visit every year. Angiographic follow clinically driven	100
Jimenez-Navarro, 2004	FFR	Death, Cardiac Death, MI, any revascularization, LM revascularization	Clinical visits or telephone interviews	100
Legutko, 2005	FFR	Death, MI, any revascularization, LM revascularization	Clinical visits	100
Lindstaedt,2006	FFR	Death, MI, any revascularization, LM revascularization	Telephone interviews	100
De La Torre Hernandez (LITRO), 2011	IVUS	Death, Cardiac Death MI, any revascularization, LM revascularization	Two and five-years follow-up were planned reviewing clinical reports or by telephone interview	100

Table A - Additional informations regarding study primary outcome and follow-up. MI: Myocardial Infarction; LM: Left Main; PCI: Percutaneous Coronary Intervention; CABG: Coronary Artery By-pass graft. Part1

De la Torre Hernandez, 2007	IVUS	Death, Cardiac Death, MI, any revascularization, LM revascularization	Planned reviewing clinical reports or by telephone interview	100
Fassa, 2005	IVUS	Death, MI and TVR (defined as a PCI of the LM or CABG to the left coronary system due to progression of the LM disease),	Hospital records	86.4
Okabe, 2008	IVUS	Death, MI, any revascularization, LM revascularization	Telephone contact	100
Abizaid, 1999	IVUS	Death, Cardia Death MI, any revascularization, LM revascularization	Serial telephone interviews 1, 3, 6 and 12 months from baseline	98

Table A - Additional informations regarding study primary outcome and follow-up. MI: Myocardial Infarction; LM: Left Main; PCI: Percutaneous Coronary Intervention; CABG: Coronary Artery By-pass graft. Part2

FFR STUDIES					
STUDY	**LM ambiguous stenosis definition for study inclusion**	**Mean reference diameter (mm)**	**Mean MLD (mm)**	**Mean DS (%)**	**LM stenosis location**
Bech, 2001	- Visual estimation stenosis 40-60% Or - LM stenosis not quantifiable by visual estimation	- 4.06 (FFR ≥0.75) -3.45 (FFR <0.75)	- 2.35 (FFR ≥0.75) - 1.95 (FFR <0.75)	- 42 (FFR ≥0.75) - 43 (FFR <0.75)	Unknown
Courtis, 2009	- equivocal LM suspected but not quantifiable from the angiogram Or - intermediate (30% to 60% diameter stenosis by visual estimation)	3.64 ± 0.77	2.08 ± 0.59	42± 13	Ostium-body (28%) Distal (63%) Diffuse (9%)
Hamilos, 2009	- equivocal left main at visual estimation	4.04±1.03 (FFR ≥0.80) 3.8±0.8 (FFR <0.80)	2.6±0.66 (FFR ≥0.80) 2.01±0.49 (FFR <0.80)	34.7±12 (FFR ≥0.80) 44.2±12.6 (FFR <0.80)	Ostial 35% (FFR ≥0.80) 41% (FFR <0.80) Mid 14% (FFR ≥0.80) 8% (FFR <0.80) Distal 52% (FFR ≥0.80) 51% (FFR <0.80)
Jasti, 2004	-angiographic ambiguous left main	4.21±1.0	2.14±0.86	49±15	Ostial 36.4% Mid 5.4% Distal 58.2%
Jimenez-Navarro, 2004	- stenosis of moderate severity (visual estimation 30-50%)	3.57 ±0.69 (FFR ≥0.75) 3.22 ±0.31 (FFR <0.75)	2.21± 0.61 (FFR ≥0.75) 1.8± 0.46 (FFR <0.75)	34.21±11.4 (FFR ≥0.75) 43.86±12.1 (FFR ≥0.75)	Unknown
Legutko, 2005	-borderline LM stenosis: 30% to 60% on visual assessment	3.89±0.62 (FFR ≥0.75) 3.54±0.7 (FFR <0.75)	2.24±0.49 (FFR ≥0.75) 1.84±0.45 (FFR <0.75)	43±7 (FFR ≥0.75) 46±13 (FFR <0.75)	Proximal 45% (FFR ≥0.75) 28% (FFR <0.75) Mid 5%(FFR ≥0.75) 17% (FFR <0.75) Distal 35% (FFR ≥0.75) 44% (FFR <0.75)
Lindstaedt,2006	- 40% to 80% stenosis by visual estimation or - LMCA disease was suspected but could not be quantified from the angiogram	3.92 Non surgical group 3.37 Surgical group	2.31 Non surgical group 1.96 Surgical group	44 Non surgical group 45 Surgical group	Ostial 20.8% Non surgical group 40.7% Surgical Group

Table B - LM angiographic features in FFR and IVUS studies.

IVUS STUDIES					
STUDY	**LM definition for study inclusion**	**Mean reference diameter (mm)**	**Mean MLD (mm)**	**Mean DS (%)**	**LM stenosis location**
De La Torre Hernandez (LITRO), 2011	-uncomplicated (no ulceration, dissection, or thrombus) intermediate (25% to 60% visual stenosis) unprotected LM lesions	3.9±0.8 Deferred group 3.6±0.8 Revascularized group	2.5±0.6 Deferred group 2.3±0.7 Revascularized group	37.2±8.0 Deferred group 47.4±10.0 Revascularized group	Ostial 41.8% Deferred group 21.7% Revascularized group Mid 23.4% Deferred group 28.9% Revascularized group Distal 34.6% Deferred group 49.3% Revascularized group
De la Torre Hernandez, 2007	-Intermediate lesion (25%-50% stenosis visualized) with an uncomplicated appearance (no ulcer, dissection, or thrombus) in an unprotected LMCA"	unknown	2.35 MLA>6 mm2 1.9 MLA≤6 mm2	38 MLA>6 mm2 45 MLA≤6 mm2	Diffuse 12.5% MLA>6 mm2 42% MLA≤6 mm2 Ostial 43.7% MLA>6 mm2 13% MLA≤6 mm2
Fassa, 2005	-undeterminate lesions	3.6 ±0.7 MLA <7.5 mm2 revasc 3.5 ±0.6 MLA <7.5 mm2 defer 4.1±0.7 MLA ≥ 7.5 mm2 revasc 4.0±0.8 MLA≥ 7.5 mm2 defer	2.3 ± 0.5 MLA <7.5 mm2 revasc 2.2 ± 0.4 MLA <7.5 mm2 defer 2.7 ± 0.6 MLA ≥ 7.5 mm2 revasc 2.6 ± 0.6 MLA≥ 7.5 mm2 defer	35.0 ± 10.7 MLA <7.5 mm2 revasc 37.0 ± 7.0 MLA <7.5 mm2 defer 33.9 ± 9.3 MLA ≥ 7.5 mm2 revasc 34.0 ± 12.1 MLA≥ 7.5 mm2 defer	Ostial 49.3 MLA <7.5 mm2 treated 58.3% MLA <7.5 mm2 deferred 52.9% MLA ≥ 7.5 mm2 treated 64.0% MLA≥ 7.5 mm2 deferred Mid 19.7% MLA <7.5 mm2 treated 8.3% MLA <7.5 mm2 deferred 11.8% MLA ≥ 7.5 mm2 treated 15.8% MLA≥ 7.5 mm2 deferred Distal 31.0% MLA <7.5 mm2 treated 33.3% MLA <7.5 mm2 deferred 35.3% MLA ≥ 7.5 mm2 treated 20.2% MLA≥ 7.5 mm2 deferred
Okabe, 2008	- angiographic moderate LMCA disease (< 50% DS)	4.1 ±1.0	2.7 ±0.7	32 ± 9	Proximal 39% Mid 10% Distal 38% Diffuse 13%
Abizaid, 1999	-patient performing angiography and IVUS on LM who did not have subsequent catheter or surgical intervention	3.91 ±0.76	2.26 ±0.82	42 ± 16	Ostial 21

Table B - LM angiographic features in FFR and IVUS studies.

	LM LESION FFR-DEFERRED (n=345; 7 studies)	LM LESION IVUS-DEFERRED (n=563; 5 studies)
Follow-up (months)	29.0 (25.1 - 32.0)	31.5 (24.0 - 40.8)
MACEs (Death, MI, LM revascularization)	43 (12.5)	77 (13.7)
All-cause-death	17 (4.9)	40 (7.1)
- Cardiac death	2 (0.6)^	12 (2.1)°
MI	6 (1.7)	3 (0.5)
LM Revascularization	20 (5.8)	34 (6.0)

*values are number and percentages or median and quartiles (1-3). MI: Acute Myocardial Infarction; LM: left main; MACE: Major Acute Cardiovascular Event
^ reported in 1 of 7 studies
° reported in 3 of 5 studies

Table C - Crude events occurrences. MACE: major adverse cardiac events; MI: myocardial infarction related to LM; LM: left main coronary artery.

Moderator	**IVUS studies**		**FFR studies**	
	Slope(β)	p-value for interaction	Slope(β)	p-value for interaction
Age	**0.4**	**0.001**	-0.10	0.22
Female sex	-0.007	0.75	-0.07	0.33
Hypertension	0.01	0.59	-0.04	0.06
Smoke habit	-0.06	0.48	0.01	0.61
Dyslipidemia	0.0005	0.87	-0.04	0.13
Diabetes mellitus	-0.05	0.31	-0.01	0.54
MLD QCA	0.23	0.90	0.007	0.99
MLA IVUS	-0.35	0.15	-	-
Multivessel disease	0.05	0.10	-0.004	0.79
Distal LM lesion	0.02	0.28	**0.06**	**0.01**

Table D - Metaregression (unrestricted maximum likelihood) between selected variables and overall MACEs in IVUS and FFR LM deferred-studies. Beta (β) is meta-regression coefficient, and p value (p) for interaction. MLD: minimum lumen diameter; QCA: quantitative coronary angiography; MLA: minimum lumen area; LM: left main coronary artery

2.1.3. Publication No. 3, original article

"Revascularization Deferral of Nonculprit Stenoses on the Basis of Fractional Flow Reserve: 1-Year Outcomes of 8,579 Patients"

Cerrato E, Mejía-Rentería H, Dehbi HM, Ahn JM, Cook C, Dupouy P, Baptista SB, Raposo L, Van Belle E, Götberg M, Davies JE, Park SJ, Escaned J.

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Summary: in patients with stable angina pectoris (SAP), clinical practice guidelines[1,2] recommend the use of coronary physiology to decide if revascularization of intermediate severity coronary stenosis is indicated. In these patients, the use of FFR has been shown to be safe[3–5]. With growing adoption of coronary physiology, FFR is also increasingly being used to guide revascularization in patients with ACS, particularly to assess the functional relevance of non-culprit vessels in patients with multivessel disease (MVD). In this pooled analysis of individual patient data (8579 patients) from 5 international studies, we investigated the safety of FFR-based revascularization deferral of non-culprit lesions in patients with ACS compared with stable angina patients (SAP). Data from 3 international large database along with 2 RCT trials with similar design and endpoind were collected and pooled together aiming to assess 1-year occurrence of MACE (composite of death, nonfatal myocardial infarction, or unplanned revascularization)

At 1-year, the deferred-ACS group presented a higher MACE occurrence compared to the deferred-SAP group (4.46% vs. 2.83%, adjusted HR 1.72, 95% CI 1.17-2.53, p<0.01). This difference was mainly driven by an excess of unplanned revascularization. However, no differences were found in the treated groups according to clinical presentation (MACE rate 6.51% vs. 6.20%, adjusted HR 1.21, 95% CI 0.88-1.26, p=0.24).

Revascularization Deferral of Nonculprit Stenoses on the Basis of Fractional Flow Reserve

1-Year Outcomes of 8,579 Patients

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ABSTRACT

OBJECTIVES The aim of this study was to evaluate the safety of revascularization deferral on the basis of fractional flow reserve interrogation of nonculprit lesions in patients with acute coronary syndromes (ACS).

METHODS A pooled analysis was performed of individual patient data included in 5 large international published studies on physiology-guided revascularization. The primary endpoint was major adverse cardiac events (MACE) (a composite of death, nonfatal myocardial infarction, or unplanned revascularization) at 1-year follow-up. Clinical outcomes of patients with ACS and stable angina pectoris (SAP) were compared in both the deferred and the revascularized groups.

RESULTS A total of 8,579 patients were included in the analysis, 6,461 with SAP and 2,118 with ACS and nonculprit lesions. Using fractional flow reserve, revascularization was deferred in 5,129 patients (59.8%) and performed in 3,450 patients (40.2%). In the deferred ACS group, a higher MACE rate was observed compared with the deferred SAP group (4.46% vs. 2.83%; adjusted hazard ratio [HR]: 1.72; 95% confidence interval [CI]: 1.17 to 2.53; $p < 0.01$). Both early unplanned revascularization (3.34% and 2.04% in ACS and SAP; adjusted HR: 1.81; 95% CI: 1.09 to 3.00; $p = 0.02$) and mortality (0.86 % and 0.56% in ACS and SAP; adjusted HR: 1.60; 95% CI: 0.68 to 3.79; $p = 0.28$) contributed to this excess in MACE. On the contrary, no differences in outcomes linked to clinical presentation were found in treated patients (MACE rate 6.51% vs. 6.20%; adjusted HR: 1.21; 95% CI: 0.88 to 1.26; $p = 0.24$).

CONCLUSIONS Patients with ACS in whom revascularization of nonculprit lesions was deferred on the basis of fractional flow reserve have more MACE at 1 year compared with patients with SAP with deferred revascularization. Unplanned revascularization mainly contributed to this excess of MACE. (J Am Coll Cardiol Intv 2020;■:■–■)

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ABBREVIATIONS AND ACRONYMS

ACS = acute coronary syndrome(s)

CI = confidence interval

FFR = fractional flow reserve

HR = hazard ratio

MACE = major cardiac adverse event(s)

MI = myocardial infarction

NCL = nonculprit lesion

NSTEMI = non-ST-segment elevation myocardial infarction

PCI = percutaneous coronary intervention

RCT = randomized controlled trial

SAP = stable angina pectoris

STEMI = ST-segment elevation myocardial infarction

In patients with stable angina pectoris (SAP), clinical practice guidelines recommend the use of coronary physiology to decide if revascularization of intermediate-severity coronary stenosis is indicated (1,2). In these patients, the use of fractional flow reserve (FFR) has been shown to be safe (3–5). With the growing adoption of coronary physiology, FFR is also increasingly being used to guide revascularization in patients with acute coronary syndromes (ACS), particularly to assess the functional relevance of nonculprit vessels in patients with multivessel disease. Available evidence, including randomized controlled trials (RCTs) (6,7), supports the use of FFR guidance in ACS nonculprit stenoses compared with culprit-only treatment. Moreover, the use of FFR has demonstrated better outcomes with respect to angiography-only approaches in both ACS and SAP (8).

Despite this, few data are available regarding the comparative performance of FFR in ACS versus SAP. Although some studies support the reliability of FFR measurements in patients with ACS, a number of studies have consistently reported poorer clinical outcomes in patients in whom revascularization was deferred on the basis of FFR measurements (6,7,9,10), both with respect to previously published data collected in patients with SAP (3–5) and in the case of direct comparison with a SAP group (11). However, drawing firm conclusions on the basis of these data is hampered by small sample sizes and major methodological differences among studies.

Considering this background, the aim of the present study was to investigate the safety of revascularization deferral of nonculprit lesions (NCLs) in patients with ACS in a large study population, obtained from 3 large observational studies and 2 RCTs.

METHODS

STUDY DESIGN. We performed a pooled analysis of individual patient data from 3 observational prospective multicenter studies and 2 RCTs in which FFR was used to guide revascularization. Characteristics of the studies included are summarized in **Figure 1**. The R3F (French FFR Registry) (12), POST-IT (Portuguese Study on the Evaluation of FFR Guided Treatment of Coronary Disease) (13), and IRIS-FFR (14) registries prospectively enrolled patients with at least 1 coronary lesion with FFR measurement from 2005 to 2015. These 3 nationwide prospective studies share a common design and objective, dedicated to investigating the routine use of FFR at the time of diagnostic angiography and its impact on patient management decisions and on 1-year clinical outcomes. Contrary to R3F and POST-IT, in IRIS-FFR revascularization was generally recommended when FFR was <0.75 and deferred when FFR was >0.80. For FFR values between 0.75 and 0.80, the decision regarding revascularization was left to the operator's discretion.

DEFINE-FLAIR (Functional Lesion Assessment of Intermediate Stenosis to Guide Revascularisation) (15) was a multicenter, international, randomized trial in which instantaneous wave-free ratio was compared with FFR for physiologically guided coronary revascularization and for which the adjudication of the study endpoints was blinded for group allocation. A total of 1,250 patients were enrolled in the FFR group. Similarly, the iFR-SWEDEHEART (Instantaneous Wave-Free Ratio Versus Fractional Flow Reserve in Patients With Stable Angina Pectoris or Acute Coronary Syndrome) trial (16) was a multicenter, randomized, controlled, open-label clinical trial investigating the merit of instantaneous wave-free ratio or FFR in guiding coronary revascularization. The FFR arm included 1,018 patients.

Among all of the patients enrolled in these 5 studies, the present patient-level analysis included all the cases in which: 1) FFR was performed to interrogate NCLs in patients presenting with ACS or any lesion in patients presenting with SAP; 2) revascularization decision making was based upon the FFR value (cutoff 0.80); and 3) 1-year follow-up was available. In cases of multiple vessel interrogations within the same patient, the subject was considered deferred if all lesions were deferred. Conversely, the subject was considered revascularized if at least 1 interrogated stenosis was treated.

The primary endpoint of the present analysis was the 1-year incidence of major adverse cardiac events (MACE), a composite of all-cause death, nonfatal myocardial infarction (MI), or unplanned

The authors attest they are in compliance with human studies committees and animal welfare regulations of the authors' institutions and Food and Drug Administration guidelines, including patient consent where appropriate. For more information, visit the *JACC: Cardiovascular Interventions* author instructions page.

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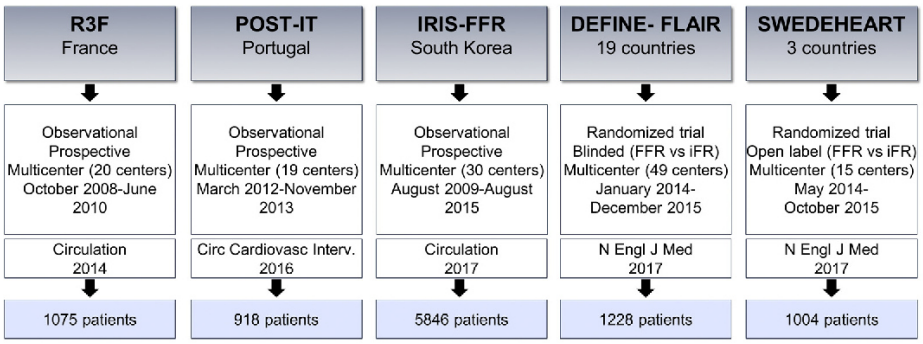
FIGURE 1 Characteristics of the Studies Included in the Pooled Patient-Level Analysis



DEFINE-FLAIR = Functional Lesion Assessment of Intermediate Stenosis to Guide Revascularisation; FFR = fractional flow reserve; iFR = instantaneous wave-free ratio; iFR-SWEDEHEART = Instantaneous Wave-Free Ratio Versus Fractional Flow Reserve in Patients With Stable Angina Pectoris or Acute Coronary Syndrome; POST-IT = Portuguese Study on the Evaluation of FFR Guided Treatment of Coronary Disease; R3F = French FFR Registry.

revascularization. Revascularization was considered to be unplanned when it was not either performed or planned during the index procedure as part of a staged procedure. Secondary study endpoints were the individual components of the primary endpoint in the same study population at 1 year. MI definitions across different studies are reported in Supplemental Table 1. Ethical approval was obtained before the publication of each study included.

STATISTICAL ANALYSIS. Categorical and binary variables were compared between groups using chi-square tests. Continuous variables were compared using Student's *t*-test or the Wilcoxon signed rank test in case of a non-normal distribution. For MACE and its components, time-to-event analyses were performed. We fitted mixed-effect Cox survival models with a random intercept per study and a random effect of ACS versus SAP for each study, adjusting with fixed effects for the following covariates: age, sex, diabetes, current smoking, hypertension, hyperlipidemia, and previous MI. Testing of validity of the proportional hazard assumption was done using Schoenfeld residuals. There were no signs of violations of proportional hazards assumption. Results are reported using hazard ratios (HRs), 95% 2-sided confidence intervals (CIs), and cumulative hazard curves.

The primary endpoint is reported for the FFR-deferred and FFR-treated groups separately. In the FFR-deferred group, a post hoc landmark analysis was performed for MACE using 1 month of follow-up as the cutoff. This means that we have fitted a survival model for the dataset up to 1 month, and a model for the dataset from 1 month onward, for patients still at risk at 1 month.

All analyses were carried out using Stata version 15.1 (StataCorp, College Station, Texas) and R version 3.4.3 (R Foundation for Statistical Computing, Vienna, Austria). A p value of <0.05 was considered to indicate statistical significance.

RESULTS

STUDY POPULATION. Databases were obtained anonymously by each lead investigator of the included studies. First, data were extracted from each database performing a quality control with the aim of harmonizing variables and data needed. In case of discrepancy or missing information, queries were sent to investigators. In the second step, all data were pooled together, generating a patient-oriented and a vessel-oriented database in order to uniformly report baseline and procedural features. Inclusion and exclusion criteria for each record were verified. Among the total of 10,019 patients collected in the pooled database, 1,440 were excluded from the analysis because physicians did not follow FFR results to perform or defer revascularization. Accordingly, 5,129 patients with deferred revascularization (ACS, n = 1,166) and 3,450 treated patients (ACS, n = 952) were included. Follow-up data were obtained pooling together the 12-month event rate. Patient-level demographic, angiographic, and procedural data are summarized in Table 1. A typical distribution

TABLE 1 Baseline and Procedural Characteristics According to FFR-Based Decision Making and Clinical Presentation

	Deferred (n = 5,129)			Treated (n = 3,450)		
	ACS (n = 1,166)	SAP (n = 3,963)	p Value	ACS (n = 952)	SAP (n = 2,498)	p Value
Age (yrs)	66.0 (58.0-74.0)	65.0 (58.0-72.0)	0.05	62.0 (54.0-70.1)	64.9 (57.7-71.7)	<0.01
Male	800 (68.6)	2,688 (67.8)	0.61	763 (80.1)	1,960 (78.5)	0.28
Type 2 diabetes mellitus	319 (27.4)	1,162 (29.3)	0.43	278 (29.2)	873 (34.9)	0.01
Hypertension	766 (65.7)	2,634 (66.5)	0.88	600 (63.0)	1,737 (69.5)	<0.01
Hyperlipidemia	683 (58.6)	2,472 (62.4)	0.03	549 (57.7)	1,751 (70.1)	<0.01
Current smoking	330 (28.3)	941 (23.7)	<0.01	317 (33.3)	617 (24.7)	<0.01
Previous MI	227 (19.5)	556 (14.0)	<0.01	193 (20.3)	443 (17.7)	0.23
Previous PCI	322 (27.6)	1,128 (28.5)	0.81	256 (26.9)	716 (28.7)	0.28
Number of vessels evaluated per patient	1.23 ± 0.53	1.34 ± 0.68	<0.01	1.67 ± 0.90	1.55 ± 0.80	<0.01
Functionally significant lesions per patient	–	–	–	1.22 ± 0.51	1.18 ± 0.45	0.02

Values are median (interquartile range), n (%), or mean ± SD.

ACS = acute coronary syndromes; FFR = fractional flow reserve; MI = myocardial infarction; PCI = percutaneous coronary intervention; SAP = stable angina pectoris.

of cardiovascular risk factors is demonstrated in both groups, with a significantly higher incidence of type 2 diabetes mellitus, hypertension, and hyperlipidemia in SAP compared with ACS. The clinical presentations of included patients according to the definitions reported in each study are available in Supplemental Table 2. In the overall study population, mean FFR was 0.83 ± 0.11. A small but statistically significant difference in FFR values was noted between the ACS and SAP groups (0.82 ± 0.11 vs. 0.83 ± 0.11; p < 0.01) (Supplemental Figure 1). Concordantly, the rate of revascularization was higher in patients presenting with ACS (n = 953 [45%]) than in the SAP group (n = 2,520 [39%]). The median follow-up time of participants was 12 months

CLINICAL OUTCOMES OF THE FFR-DEFERRED POPULATION (PRIMARY ENDPOINT). When analyzed according to FFR-based decision, deferral in patients with ACS was associated with a higher MACE rate compared with patients with SAP (4.46% vs. 2.83%; adjusted HR: 1.72; 95% CI: 1.17 to 2.53; p < 0.01) (**Table 2, Figure 2, Central Illustration**). Both early unplanned revascularization (3.34% and 2.04% in ACS and SAP; adjusted HR: 1.81; 95% CI: 1.09 to 3.00; p = 0.02) and mortality (0.86% and 0.56% in ACS and SAP; adjusted HR: 1.60; 95% CI: 0.68 to 3.79; p = 0.28) contributed to this excess in MACE. A differential rate of MI also contributed to the excess in MACE, although there was no statistical difference between the ACS and SAP groups (0.86% vs. 0.45%; adjusted HR: 2.06; 95% CI: 0.87 to 4.86; p = 0.10) (Supplemental Figures 2A to 2C). Visual analysis of the Kaplan-Meier curves revealed a marked separation of SAP and ACS curves within the first month of follow-up and up to 3 months (**Figure 2**). We performed an exploratory landmark analysis at 1 month of follow-up. In the deferred patients, the adjusted HR for clinical presentation on MACE prior to 1 month was 2.29 (95% CI: 0.82 to 6.37; p = 0.11) and after 1 month was 1.52 (95% CI: 1.05 to 2.20; p = 0.03). In other words, the effect of clinical presentation was slightly more pronounced (although not reaching statistical significance) during the course of the first month of follow-up than during the rest of the follow-up. A similar rate of MACE was observed repeating the analysis excluding patients with SAP with single-vessel disease (Supplemental Figure 3).

CLINICAL OUTCOMES OF THE FFR-REVASCULARIZED POPULATION. Among patients revascularized according to FFR ≤0.80, the rate of MACE at 1 year was not significantly different between patients with ACS and those with SAP (6.51% vs. 6.20%; adjusted HR: 1.21; 95% CI: 0.88 to 1.26; p = 0.24) (**Table 3, Central Illustration**, Supplemental Figure 4). Similarly, the components of MACE at 1 year were similar between patients with ACS and those with SAP: death, 1.16% versus 0.72% (adjusted HR: 1.75; 95% CI: 0.71 to 4.33; p = 0.23); MI, 2.31% versus 1.64% (adjusted HR: 1.34; 95% CI: 0.78 to 2.31; p = 0.29); and unplanned revascularization, 4.31% versus 4.60% (adjusted HR: 1.07; 95% CI: 0.72 to 1.58; p = 0.75) (Supplemental Figures 5A to 5C).

OVERALL POPULATION ANALYSIS. One-year outcomes according to the deferral or performance of revascularization regardless of clinical presentation are reported in Supplemental Tables 2 and 3. A higher rate of MACE was observed in the treated population, driven mainly by an excess of revascularization and

MI rates. When analyzed according to clinical presentation, the overall MACE rate at 1 year was significantly higher in patients with ACS than in those with SAP (5.38% vs. 4.13%; adjusted HR: 1.37; 95% CI: 1.08 to 1.72; p = 0.01) (Supplemental Table 4, Supplemental Figure 6).

TABLE 2 Primary and Secondary Endpoints at 1 Year in Deferred Group According to Clinical Presentation (ACS vs. SAP)

	ACS (n = 1,166)	SAP (n = 3,963)	Adjusted HR (95% CI)	p Value
MACE	52 (4.46)	112 (2.83)	1.72 (1.17-2.53)*	<0.01
Death	10 (0.86)	22 (0.56)	1.60 (0.68-3.79)	0.28
Myocardial infarction	10 (0.86)	18 (0.45)	1.80 (0.76-4.27)*	0.18
Unplanned revascularization	39 (3.34)	81 (2.04)	1.81 (1.09-3.00)	0.02

Values are n (%). Results are presented for mixed-effect Cox models allowing for patients nested within studies, and a random effect for the effect of ACS versus SAP, in addition to fixed effects for the other covariates. *Adjusted for age, sex, diabetes, current smoking, hypertension, hyperlipidemia, and previous myocardial infarction.

CI = confidence interval; HR = hazard ratio; MACE = major adverse cardiac events; other abbreviations as in Table 1.

DISCUSSION

The aim of the present study was to determine the safety of FFR-guided revascularization in nonculprit stenoses in patients presenting with ACS. We found that revascularization deferral in patients with ACS was associated with higher 1-year MACE rates compared with patients presenting with SAP. The difference in MACE rate was driven predominantly by a significantly higher rate of early unplanned revascularization in patients presenting with ACS. As opposed to the revascularization deferral group, 1-year outcome in patients treated on the basis of FFR was not influenced by clinical presentation with ACS or SAP.

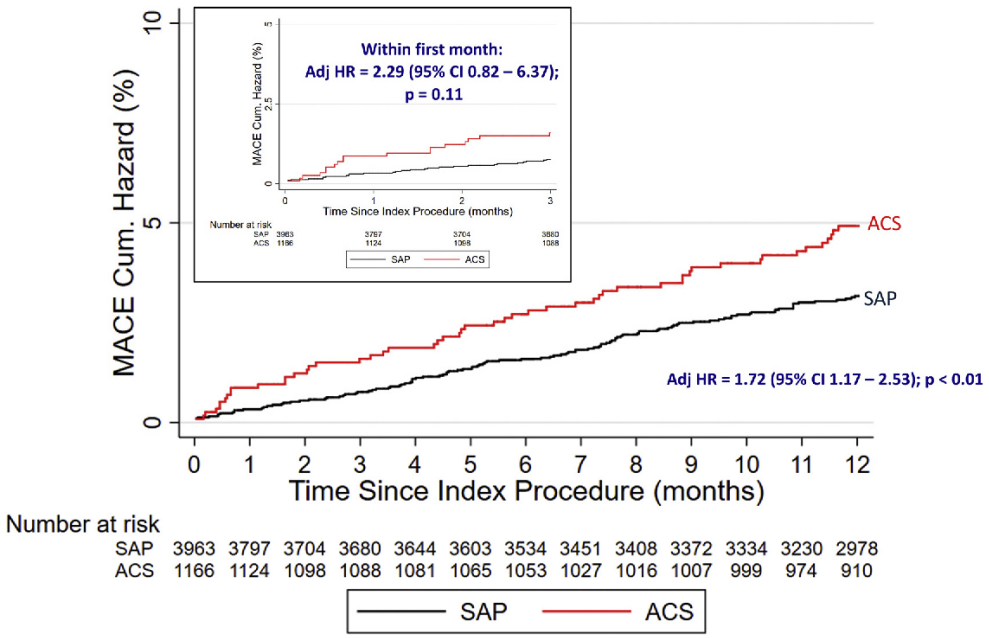
Several investigators (11,17,18) have reported the results of clinical series suggesting that, contrary to those with SAP, deferral of revascularization on the basis of FFR in patients with ACS entails a higher risk for subsequent events. Overall, these studies were based on single-center observational designs, in some occasions interrogating either culprit or nonculprit vessels. Therefore, the present study was designed to explore whether the safety of revascularization deferral in intermediate NCLs is influenced by clinical presentation, avoiding the limitations of previous studies by analyzing a large study population of patients prospectively enrolled in multicenter studies.

In the setting of ST-segment elevation MI (STEMI), the recently published COMPLETE (Complete vs Culprit-Only Revascularization to Treat Multi-Vessel Disease After Early PCI for STEMI) study (19) indicated a benefit in terms of reduction of MI when revascularization was performed in NCLs. Notably, adoption of intracoronary physiology was mandatory only in intermediate stenosis occurring, overall, in <1% of the cases. Previous studies using FFR to guide complete revascularization in patients presenting with STEMI, such as DANAMI-3-PRIMULTI (Danish Study of Optimal Acute Treatment of Patients With ST-Elevation Myocardial Infarction-Primary PCI in Patients With ST-Elevation Myocardial Infarction and Multivessel Disease: Treatment of Culprit Lesion Only or Complete Revascularization) (6) and Compare-Acute (Comparison Between FFR Guided Revascularization Versus Conventional Strategy in Acute STEMI Patients With MVD) (7), cannot be used to clarify this issue given the absence of a SAP comparator group. In a recent meta-analysis (20) of individual patient data including those 2 RCTs as well as FAME 2 (Fractional Flow Reserve [FFR] Guided Percutaneous Coronary Intervention [PCI] Plus Optimal Medical Treatment [OMT] Versus OMT) (21) trial (encompassing only patients with SAP), FFR-guided percutaneous coronary intervention (PCI) resulted in a reduction of the composite of cardiac death or MI compared with medical therapy in patients with SAP, which was driven by a decreased risk for MI. Accordingly, it remains inconclusive if physiology-guided revascularization in patients with ACS and multivessel disease will be associated with an even lower event rate than anatomically guided PCI (as has already demonstrated in the context of SAP).

In contrast to the aforementioned studies, which focused exclusively on patients with STEMI, the present analysis also included patients presenting with unstable angina or non-ST-segment elevation MI (NSTEMI). This provides valuable information regarding the performance of FFR in these frequently encountered clinical subsets. Additionally, mean FFR value in the pooled group was 0.83, mainly reflecting current real-world registries.

Several hypotheses can be put forward to explain the higher risk for MACE found in patients with deferred revascularization of ACS nonculprit stenoses. Compared with patients with SAP: 1) patients presenting with ACS may have an intrinsically higher risk for events during follow-up; 2) nonculprit vessels in patients with ACS may have more vulnerable atherosclerotic plaques, increasing the chances of a subsequent ACS; 3) misdiagnosis of the ACS culprit vessel might lead to FFR interrogation of the true culprit lesion, especially in unstable angina and NSTEMI subsets, with negative FFR resulting in deferral treatment of a high-risk stenosis; and 4) FFR

FIGURE 2 Primary Endpoint: MACE in Deferred Group

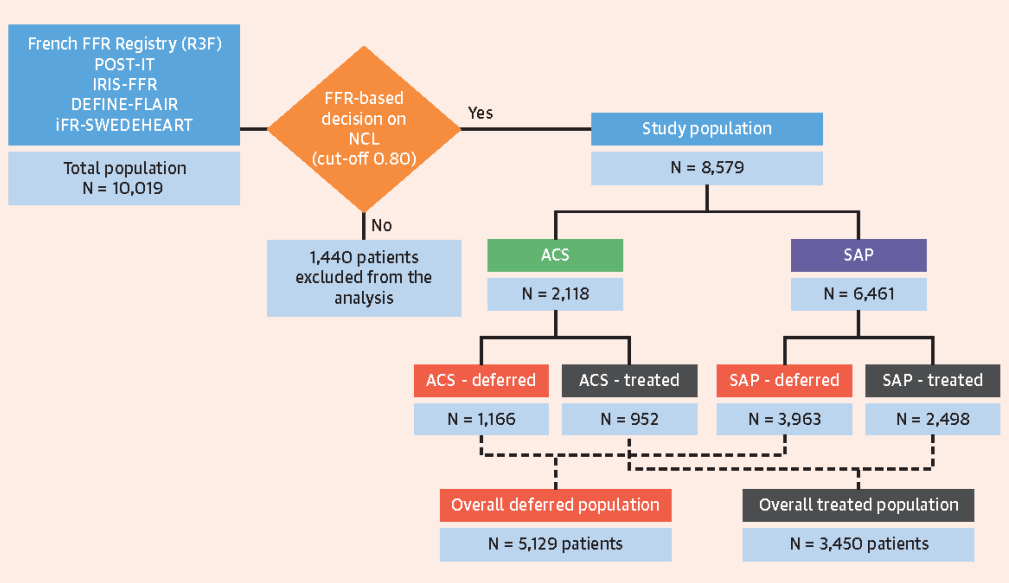


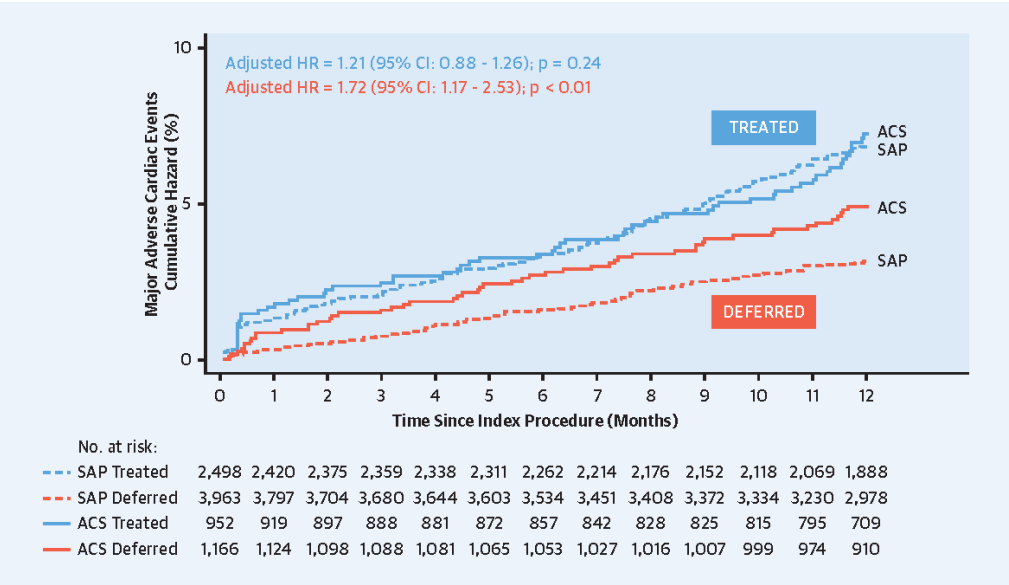
Cumulative hazard curve for major adverse cardiac events (MACE) after deferral on the basis of nonischemic fractional flow reserve >0.80 by clinical presentation. The **inset** depicts the same curve (adjusted hazard ratio [Adj HR] for clinical presentation of MACE) focusing on the first 3 months. ACS — acute coronary syndromes; CI — confidence interval; Cum. — cumulative; SAP — stable angina pectoris.

may have a lower diagnostic yield in patients with ACS because of transient modification of hemodynamic status and microcirculatory status, which may underscore the true functional impact of nonculprit stenoses in ACS. These hypotheses will be discussed later in the light of available evidence and additional findings in our study.

In agreement with previous large registries (22–24), we found worse outcomes in patients with ACS compared with those with SAP, despite the larger number of clinical risk factors in the latter group. What our study adds is that the excess of events among patients with ACS over those with SAP did not occur in patients with nonculprit stenosis treated with PCI but in those in whom nonculprit stenoses were deferred. Multiple hypotheses can explain this phenomenon. It is likely that the coronary tree of patients with ACS has more vulnerable atheroma prone to trigger cardiac events. The prognostic information provided by FFR in a vessel with vulnerable plaques refers strictly to ischemia caused by fixed stenoses and not the potential consequence of ulceration and thrombosis of vulnerable lesions present in the interrogated vessel. Ongoing studies such as COMBINE (Optical Coherence Tomography Morphologic and Fractional Flow Reserve Assessment in Diabetes Mellitus Patients) (25) are currently investigating the prognostic relevance of vulnerable atherosclerotic plaques in nonculprit vessels with FFR >0.80. However, for the present time, in the absence of flow-limiting stenosis, there is no evidence to justify the use of PCI in nonculprit vessels to prevent subsequent cardiac events. Furthermore, the fact that occurrence of unplanned revascularization within the first months mainly contributed to the excess of MACE in deferred ACS does not support the hypothesis of ACS triggered by subsequent plaque rupture, which most likely would present as MI and would be evenly distributed over follow-up. Consequently, from a clinical point of view, the early occurrence of events could potentially be explained as a consequence of persistent or recurrent angina symptoms rather than a subsequent rupture of a high-risk fibroatheroma in a vulnerable plaque triggering a

CENTRAL ILLUSTRATION **Study Design and Primary Endpoints**





Cerrato, E. et al. J Am Coll Cardiol Intv. 2020;■(■):■-■.

(Top) Design of the study. **(Bottom)** Primary endpoints. Major adverse cardiac events (MACE) in deferred and treated groups. Cumulative hazard curve for MACE after fractional flow reserve-based deferral or revascularization by clinical presentation. CI — confidence interval; HR — hazard ratio.

TABLE 3 Primary and Secondary Endpoints at 1 Year in Treated Group According to Clinical Presentation (ACS vs. SAP)

	ACS (n = 952)	SAP (n = 2,498)	Adjusted HR (95% CI)	p Value
MACE	62 (6.51)	155 (6.20)	1.21 (0.88-1.26)*	0.24
Death	11 (1.16)	18 (0.72)	1.75 (0.71-4.33)	0.23
Myocardial infarction	22 (2.31)	41 (1.64)	1.34 (0.78-2.31)*	0.29
Unplanned revascularization	41 (4.31)	115 (4.60)	1.07 (0.72-1.58)	0.75

Values are n (%). Results are presented for mixed-effect Cox models allowing for patients nested within studies, and a random effect for the effect of ACS versus SAP, in addition to fixed effects for the other covariates. *Adjusted for age, sex, diabetes, current smoking, hypertension, hyperlipidemia, and previous myocardial infarction.

Abbreviations as in Tables 1 and 2.

MI. In other words, early occurrence of unplanned revascularization could potentially have arisen from an ischemia-causing lesion that was previously deferred on the grounds of negative FFR obtained early after ACS or even some type of bias toward revascularization, which cannot be firmly excluded. Unfortunately, we can only speculate on this finding, as no additional data about those events were provided in the original studies included.

There are other potential causes for the observed excess of cardiac events in the ACS deferred group. As reported by other investigators (26), one speculative hypothesis is that occasional misdiagnosis of the culprit stenosis has occurred during the acute decision-making process. This is especially the case in patients presenting with NSTEMI or unstable angina, despite prospective study designs with clear inclusion criteria addressing this issue. However, this would not change the clinical relevance of our findings, as misdiagnosis of the ACS culprit vessel could similarly happen to any physician using FFR in patients with ACS in everyday clinical practice. Therefore, this consideration would not challenge the main message derived from the analysis of our large sample size, namely, that an FFR-based deferral of revascularization in patients with ACS has an increased risk for subsequent events compared with FFR-based deferral in patients with SAP.

Last, as previously reported by several investigators (11,26), the accuracy of FFR in predicting outcomes among patients with ACS may not be equivalent to FFR when applied in the stable setting. Mechanistically, this can be explained by a failure to achieve maximal hyperemia during ACS (which is associated with a rise in zero flow pressure and left ventricular filling pressures, enhanced sympathetic drive, and blunted coronary vasodilation) because of transient impairment of the microcirculation (27-32). Notably, decreased coronary flow reserve after an acute MI involves both culprit and nonculprit vessels, owing to the combination of post-occlusive hyperemia, myocardial necrosis, hemorrhagic microvascular injury, compensatory hyperkinesis, and neurohumoral mechanisms. A recent study performed in patients with STEMI demonstrated that nonculprit vessels frequently have microvascular and endothelial dysfunction, as assessed with coronary flow reserve, microcirculatory resistance, and acetylcholine testing (32). However, our group recently reported similar microvascular resistance, hyperemic flow, and resistive reserve ratio (a measure of myocardial hyperemia) between patients with SAP and NCLs in patients with ACS during the subacute phase of a MI (33). In this regard, recently published research (34) provides new evidence supporting the hypothesis that FFR measurements in the acute setting of ACS may lead to misclassification of the severity of nonculprit stenoses in up to 15% of cases, compared with subacute FFR measurements. Consequently, the accuracy of FFR during ACS deserves further investigation, potentially leading to the inappropriate deferral of ischemia-causing lesions.

STUDY LIMITATIONS. First, we did not systematically include all available published studies on this topic. Instead, we included studies with similar backgrounds and design, thereby collecting the largest comparison of patients managed according to FFR in NCLs in patients with ACS. Our analysis was performed at the patient level to provide the most accurate information.

Second, in patients with ACS, we cannot estimate the impact on outcome of noncardiac causes or comorbidities. However, we reported the outcomes of the treated population, in which apparently no significant differences emerged in patients with ACS compared with those with SAP. In none of the individual studies were the patients or physicians blinded as to whether deferral of revascularization had occurred. Although this might have prompted revascularization in occasional cases, we would expect that this phenomenon would occur equally in patients in stable condition and those with ACS. In this regard, one of the most important limitations of our analysis is that we cannot distinguish between unplanned revascularization occurring on a previously FFR-deferred lesion and on another de novo stenosis.

Furthermore, no data qualifying angina recurrence were available. However, these limitations are derived directly from the original studies and thus cannot be further controlled and must be interpreted with caution.

Penultimately, within the ACS group, we are unable to perform any exploratory analyses to separate NSTEMI or STEMI from unstable angina because of different definitions of clinical presentation reported in the original studies (see Supplemental Table 1). Left ventricular ejection fraction and end-diastolic pressure were not consistently recorded in the studies, precluding any adjustment of FFR measurements in our study. Unfortunately, the 2-year data from the 2 RCTs included in this study are not available yet for analysis.

Finally, the findings of the present study refer to the use of FFR as a physiological index and cannot be applied to nonhyperemic indexes used to assess nonculprit coronary arteries in patients with ACS.

CONCLUSIONS

Patients with ACS in whom revascularization of nonculprit stenoses was deferred on the basis of FFR had a higher rate of MACE at 1 year compared with those with SAP. This excess in MACE was driven by unplanned revascularization within the first months after FFR interrogation.

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PERSPECTIVES

WHAT IS KNOWN? Overall, physiology-guided coronary revascularization has been shown to improve long-term clinical outcomes. However, the safety of physiology-based revascularization deferral in patients with ACS remains controversial.

WHAT IS NEW? In this pooled analysis of individual patient data comprising 8,579 patients with FFR-guided coronary revascularization, we found a higher 1-year MACE rate in patients with ACS who underwent revascularization deferral of NCLs compared with patients with SAP who also underwent revascularization deferral. However, in patients who underwent revascularization, the MACE rate was similar regardless of clinical presentation.

WHAT IS NEXT? Further investigation is needed to determine the safety of physiology-based revascularization deferral of NCLs in patients with ACS.

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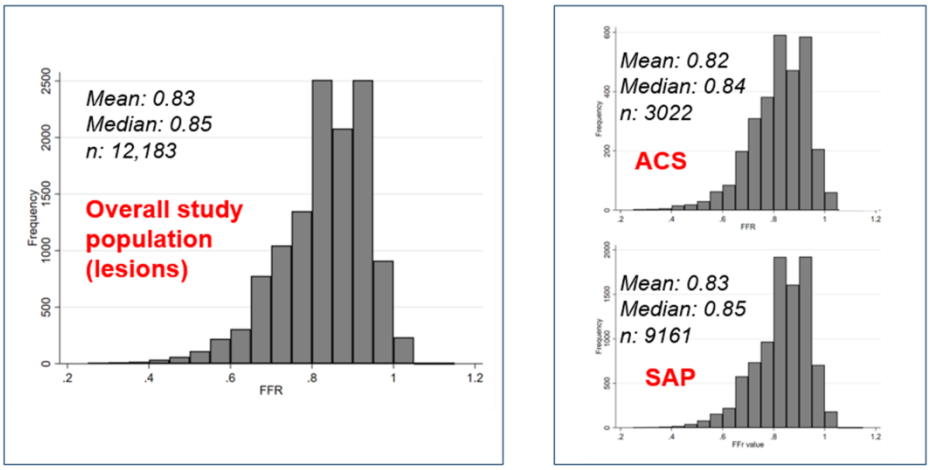
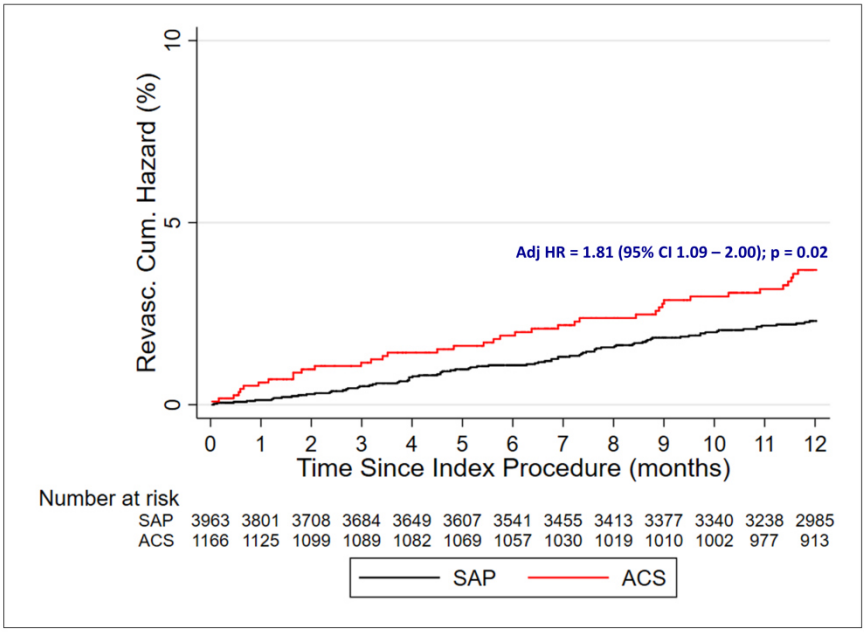
KEY WORDS acute coronary syndrome, fractional flow reserve, nonculprit stenosis

APPENDIX For supplemental tables and figures please see the online version of this paper.

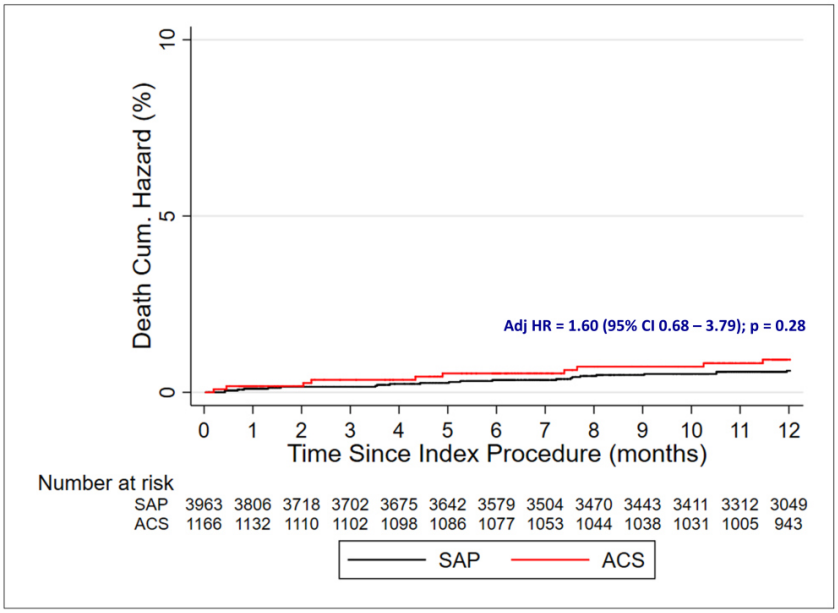
Supplementary Appendix



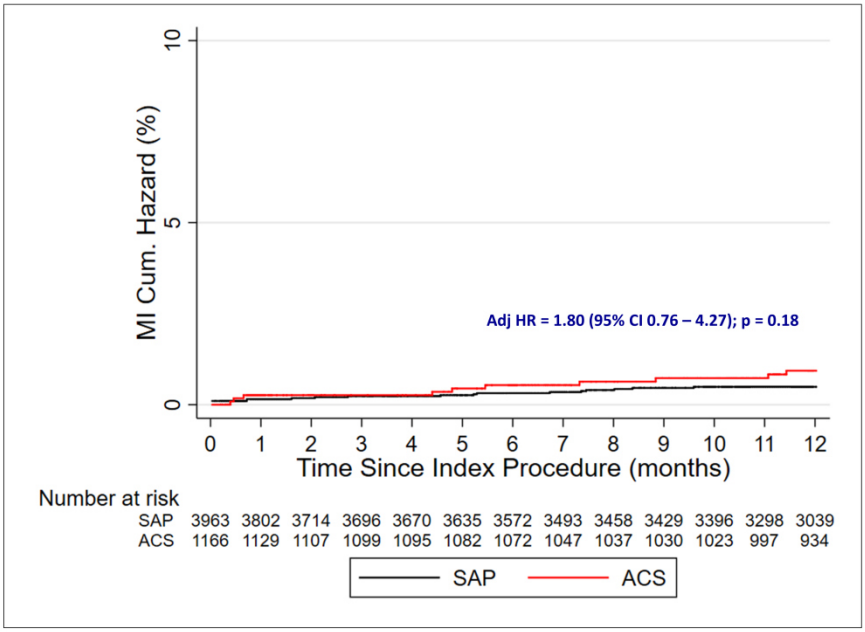
Supplemental Figure 1: FFR values distribution in ACS and SAP lesions.



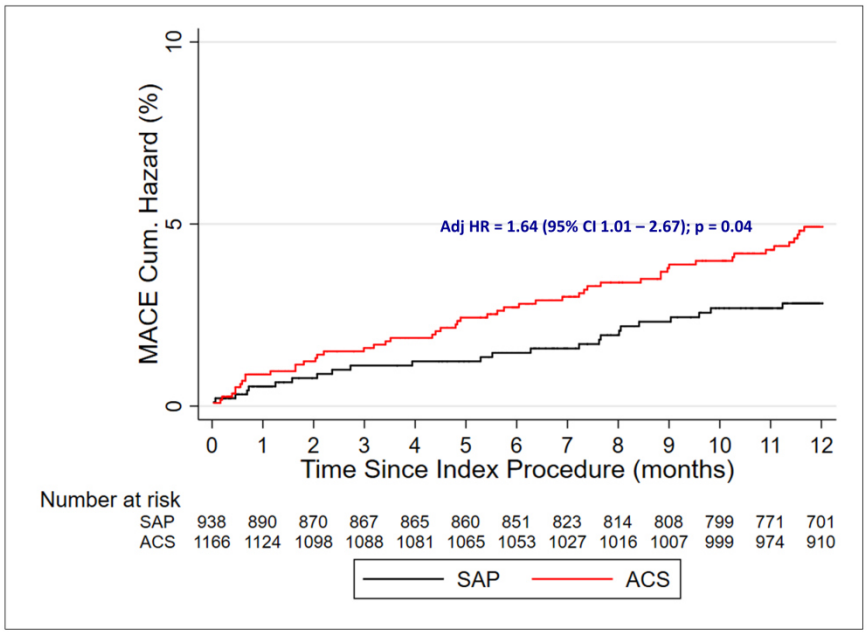
Supplemental Figure 2A. Secondary endpoint: unplanned revascularization in deferred group. Cumulative Hazard curve for Unplanned revascularization after deferral on the basis of non-ischemic FFR >0.80 by clinical presentation.



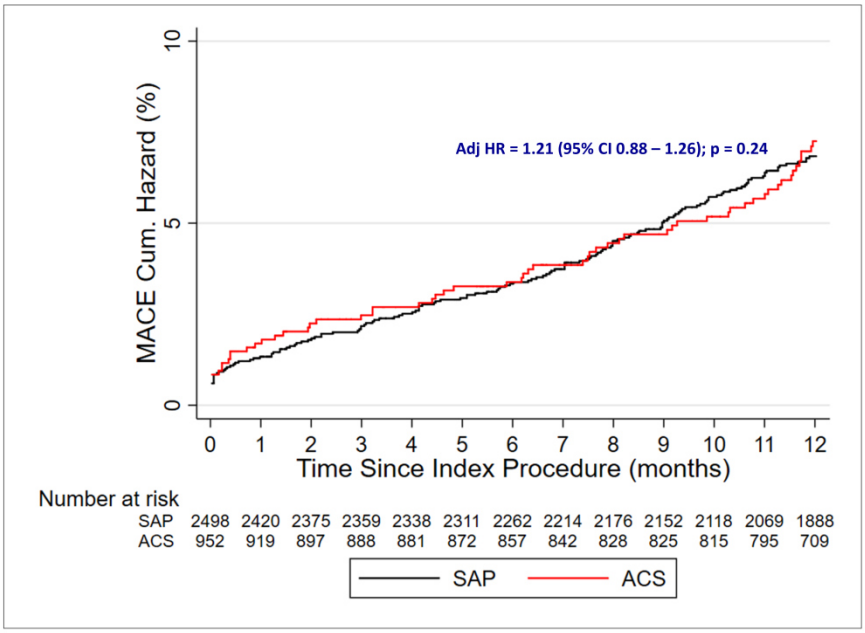
Supplemental Figure 2B. Secondary endpoint: all cause of death in deferred group. Cumulative Hazard curve for Mortality after deferral on the basis of non-ischemic FFR >0.80 by clinical presentation



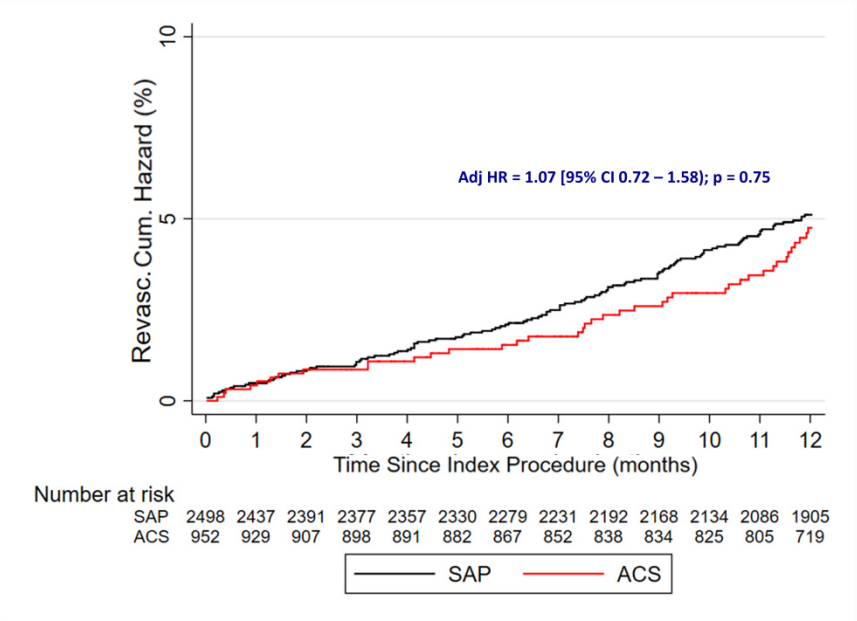
Supplemental Figure 2C. Secondary endpoint: Myocardial Infarction (MI) in deferred group. Cumulative Hazard curve for MI after deferral on the basis of non-ischemic FFR >0.80 by clinical presentation



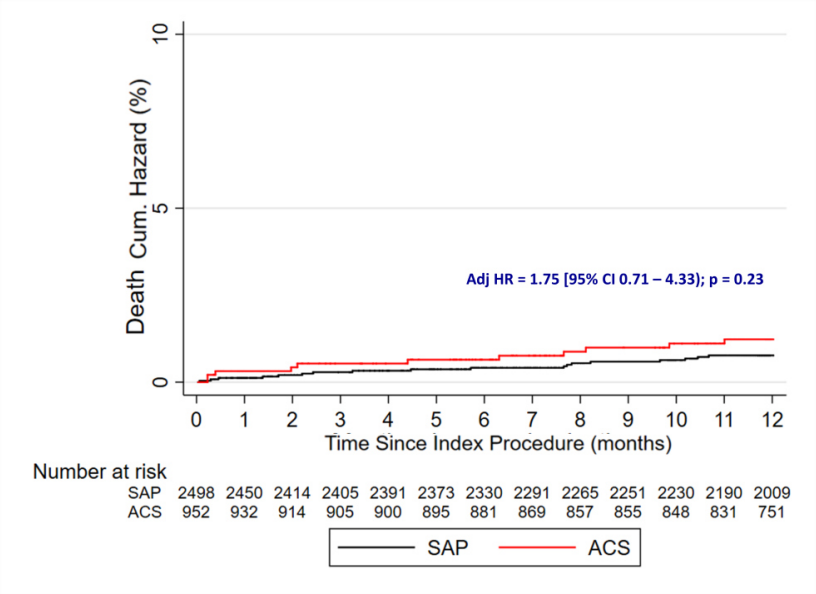
Supplemental Figure 3. MACE in deferred group including all ACS patients vs. SAP patients with multivessel disease (SAP patients with single-vessel disease was excluded)



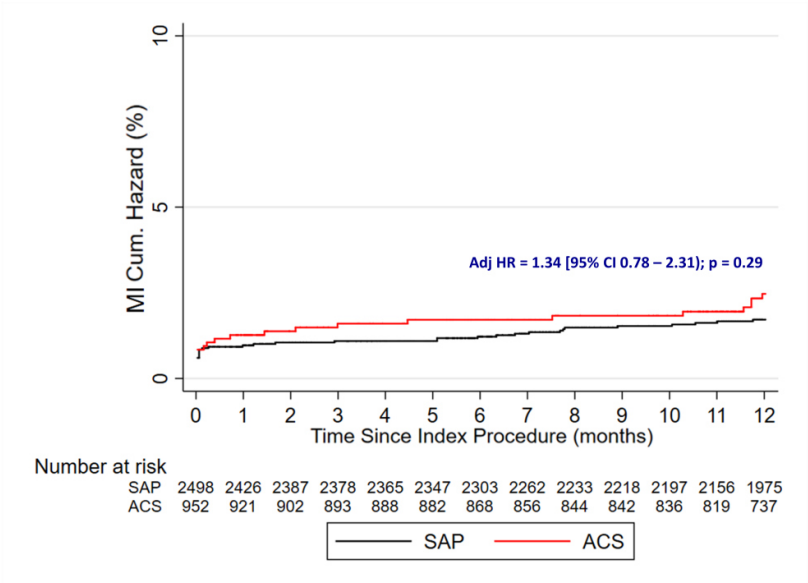
Supplemental Figure 4. Primary endpoint: MACE in treated group. Cumulative Hazard curve for MACE after treating a patient on the basis of ischemic FFR ≤ 0.80 by clinical presentation



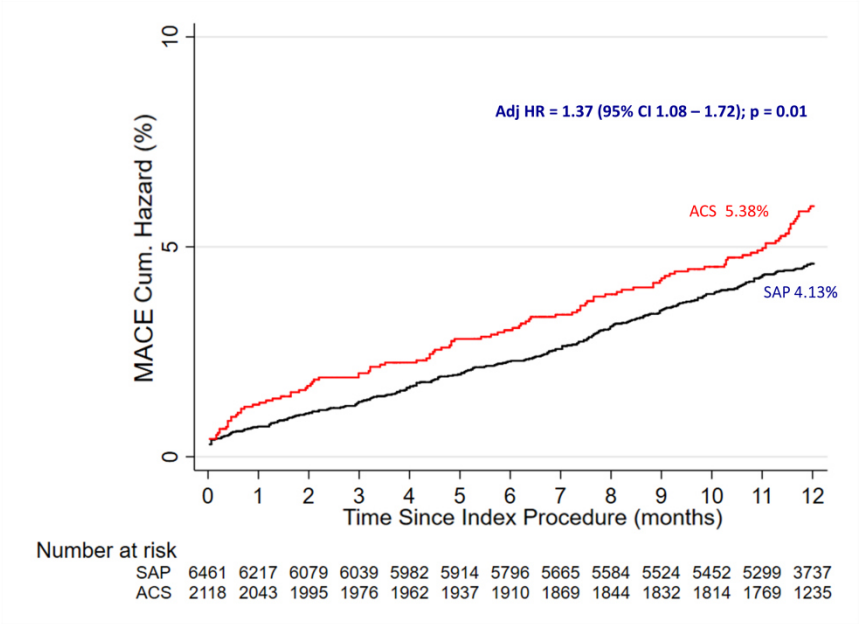
Supplemental Figure 5A. Secondary endpoint: unplanned revascularization in treated group. Cumulative Hazard curve for Unplanned revascularization after treatment on the basis of non-ischemic FFR <= 0.80 by clinical presentation.



Supplemental Figure 5B. Secondary endpoint: all cause of death in treated group. Cumulative Hazard curve for all cause of death after treatment on the basis of non-ischemic FFR <= 0.80 by clinical presentation



Supplemental Figure 5C. Secondary endpoint: Myocardial Infarction (MI) in treated group. Cumulative Hazard curve for MI after treatment on the basis of non-ischemic FFR <= 0.80 by clinical presentation



Supplemental Figure 6. Cumulative Hazard curve for overall MACE in overall study population (deferred and treated) according to clinical presentation (ACS vs SAP)

DEFINE-FLAIR, SWEDEHEART	Spontaneous MI is considered an event after the first 48 hours after PCI and after 7 days following CABG unrelated to the procedure and is defined as either: 1) Typical rise and gradual fall (troponin) or more rapid rise and fall (CK-MB) of biochemical markers of myocardial necrosis with at least one of the following: a) Ischaemic symptoms; AND/OR b) Development of new pathologic Q-waves on the ECG; AND/OR c) ECG changes indicative of ischemia (ST segment elevation or depression); OR 2) Development of new pathologic Q-waves on follow-up ECG in the absence of Cardiac biomarker assessment during the acute event. OR 3) Pathological findings of an acute MI
IRIS-FFR	Myocardial infarction was defined as follows: ≥48 hours after the procedure: any creatinine kinase -MB or troponin level increase above the upper normal limit accompanied by ischemic symptoms
POST-IT R3F	Myocardial infarction was defined according to the third 2012 ESC/ACCF/AHA/WHF (European Society of Cardiology/ American College of Cardiology Foundation/American Heart Association/World Heart Federation). Detection of rise and/or fall of cardiac biomarkers (preferably troponin) with at least one value above the 99th percentile of the upper reference limit (URL) together with evidence of myocardial ischemia with at least one of the following: 1.Symptoms of ischemia; 2. ECG changes indicative of new ischemia (new ST-T changes or new left bundle branch block [LBBB]); 3.Development of pathological Q waves in the ECG; 4. Imaging evidence of new loss of viable myocardium or new regional wall motion abnormality 5. Identification of an intracoronary thrombus by angiography or autopsy

Supplemental Table 1. Myocardial infarction definitions across different studies

DEFINE-FLAIR	**Deferred (N=562)**	**Treated (N=471)**
>48 h post STEMI	18 (3.2 %)	16 (3.4 %)
ACS	49 (8.7 %)	66 (14.0 %)
SAP	495 (88.1 %)	389 (82.6 %)
SwedeHeart	**Deferred (N=415)**	**Treated (N=423)**
NSTEMI	51 (12.3 %)	65 (15.4 %)
Unstable angina	93 (22.4 %)	86 (20.3 %)
SAP	271 (65.3 %)	272 (64.3 %)
IRIS-FFR	**Deferred (N=3113)**	**Treated (N=1771)**
STEMI	37 (1.2 %)	30 (1.7 %)
NSTEMI	120 (3.9 %)	94 (5.3 %)
Unstable angina	521 (16.7 %)	384 (21.7 %)
SAP	2435 (78.2 %)	1263 (71.3 %)
POST-IT	**Deferred (N=473)**	**Treated (N=376)**
Recent ACS	50 (10.6 %)	40 (10.6 %)
Ongoing ACS	132 (27.9 %)	84 (22.3 %)
SAP	291 (61.5 %)	252 (67.0 %)
R3F	**Deferred (N=566)**	**Treated (N=409)**
ACS	95 (16.8 %)	87 (21.3 %)
SAP	471 (83.2 %)	322 (78.7 %)

Supplemental Table 2. Clinical presentation of included patients according to each study

Outcome	Deferred N = 5129	Treated N = 3450	Adjusted HR* [deferred vs treated] (95% CI)	P-value
MACE	**164 (3.20%)**	**217 (6.29%)**	**0.54 (0.43 to 0.67)**	**<0.01**
Death	**32 (0.62%)**	**29 (0.84%)**	**0.70 (0.41 to 1.20)**	**0.20**
Myocardial infarction	**28 (0.55%)**	**63 (1.83%)**	**0.28 (0.17 to 0.46)**	**<0.01**
Unplanned revascularization	**120 (2.34%)**	**156 (4.52%)**	**0.58 (0.45 to 0.75)**	**<0.01**

Supplemental Table 3. Outcomes at 1 year according to FFR-guided decision making using the FFR cut-off 0.80 in Deferred and Treated population
MACE means the composite of death, myocardial infarction, or any revascularization at 1 year of follow up.
* adjusted for age, gender, diabetes, current smoking, hypertension, hyperlipidemia and previous MI.

Outcome	ACS N = 2118	SAP N = 6461	Adjusted HR* (95% CI)	P-value
MACE	**114 (5.38%)**	**267 (4.13%)**	**1.37 (1.08 to 1.72)**	**0.01**
Death	**21 (0.99%)**	**40 (0.62%)**	**1.44 (0.81 to 2.55)**	**0.21**
Myocardial infarction	**32 (1.51%)**	**59 (0.91%)**	**1.77 (1.11 to 2.81)**	**0.02**
Unplanned revascularization	**80 (3.78%)**	**196 (3.03%)**	**1.30 (0.99 to 1.72)**	**0.06**

Supplemental Table 4. Outcomes at 1 year in ACS vs. SAP according to FFR-guided coronary revascularization using the cut-off 0.80 in ACS and SAP population.
ACS means acute coronary syndrome; CI, confidence interval; HR, hazard ratio; SAP, stable angina pectoris, MACE: Major Adverse Cardiovascular Events; MI: Myocardial Infarction
* adjusted for age, gender, diabetes, current smoking, hypertension, hyperlipidemia and previous MI.

2.2 Microvascular Disease and Clinical Outcome

2.2.1. Publication No. 4, review article

"Evaluation of Microvascular Disease and Clinical Outcomes"

Broyd CJ, Echavarria-Pinto M, **Cerrato E,** Escaned J**.** Evaluation of Microvascular Disease and Clinical Outcomes.

Interv Cardiol Clin. 2015;4(4):443-457. doi:10.1016/j.iccl.2015.06.005

Summary: Currently, intracoronary wire-bases physiology indices are an excellent tool for the assessment of epicardial stenosis but were unable to provide accurate information on the microcirculation status. Differently from the large capacitance vessels of the epicardium, the microcirculation has a highly dynamic role in coronary blood flow and is regulated through several mechanisms including metabolic, myogenic, endothelial and neural components.

For a clinical standpoint, if concomitant microvascular disease could be identified and quantified, a more comprehensive and accurate clinical picture could be established, helping in diagnostic and therapeutic process. To date there are several proposed methods to allow intravascular quantification of microvasculature, exploring different domains. In this review we summarized these techniques along with the prognostic information provided by these modalities.

Evaluation of Microvascular Disease and Clinical Outcomes

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KEYWORDS

• Microvasculature • Intravascular • Physiology • Outcomes

KEY POINTS

- Myocardial blood supply is controlled through an interplay of metabolic, myogenic, endothelial, and neural factors; all of which may be involved in its dysfunction.
- Intravascular physiology allows the exploration of the microvascular domain in heart disease and has the potential to obtain information with prognostic relevance.
- Because interrogation of the microvasculature using intravascular techniques allows real-time assessment, it can potentially guide intracoronary adjuvant therapy, particularly during acute coronary syndromes.
- Most intravascular microcirculatory assessment tools are based on measures of coronary flow, either alone (resting flow profile) or in combination with pressure during rest (wave intensity analysis) or hyperemia to provide downstream information.
- The selection of a method to interrogate the coronary microcirculation should be based on the suspected dominant cause of dysfunction.

INTRODUCTION

Unlike the large capacitance vessels of the epicardium, the microcirculation has a highly dynamic role in coronary blood flow and is regulated through metabolic, myogenic, endothelial, and neural influences to provide the dominant component of coronary resistance.[1,2] Microcirculatory abnormalities can arise through any of these pathways, either alone or in combination, and may convey an adverse prognosis equivalent to frank obstructive epicardial vessel disease. In addition to such marked complexity in its physiologic organization and pathophysiologic potential, it anatomically consists of vessels that are less than 300 μm in diameter that escape the spatial resolution available at coronary angiography. Therefore, although assessment of the microcirculation is essential for modern cardiologic practice, it requires tools that are both sophisticated and dynamic even though they are unable to operate with direct visualization.

At present, the most widely used intravascular investigative technique is fractional flow reserve (FFR). Although this is an excellent tool for the assessment of epicardial stenosis, it is unable to provide information on the microcirculation and, therefore, cannot offer a complete cardiac assessment of the patient in the catheter laboratory. If concomitant microvascular disease could also be quantified, a more satisfactory clinical picture could be established, which would not only aid with diagnoses but also guide immediate changes in treatment and provide an individually tailored approach.

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Additionally, although in stable patients it is possible to gain some of this additional information through other investigative modalities performed at a separate time, situations in which time is a determinant of prognosis implementation of ad hoc therapy (eg, intracoronary pharmacotherapy or thrombus aspiration during ST-elevation myocardial infarction [STEMI]) requires immediate microcirculatory quantification. A periprocedural intravascular assessment technique is optimal in this setting because results can be acted on during this short therapeutic window.

Important in the treatment of microvascular dysfunction is that this may result from several potential mechanisms, including endothelial abnormalities, arteriolar or capillary remodeling, and extravascular compression. At present, there are several methods that allow such intravascular quantification of the microvasculature, each with specific advantages for exploring these respective domains (Fig. 1). This article highlights these techniques along with the prognostic information provided by these modalities.

DIRECT ANGIOGRAPHIC ASSESSMENT

The first attempts to obtain information on the microvasculature at the time of angiography began with quantification of the radiographic density of dye as it passed through the coronary system using digital extraction technology to map its timing. This predicted the resting flow rate reasonably well and recognized an impairment of coronary flow reserve (CFR) in patients with significant coronary stenosis[3] (Fig. 2).

The investigators of the Thrombolysis in Myocardial Infarction (TIMI) trials introduced several methods to objectively stratify coronary blood flow and thus assess microvascular health. The thrombolysis in myocardial infarction (TIMI)-flow grade is a qualitative assessment that uses contrast injected into the artery of interest and correlating it with resting flow rates from Doppler-flow wires.[4] It is relatively specific, with only TIMI-flow grade 3 displaying a normal underlying blood velocity. As such, the TIMI-flow grade after a treated myocardial infarction is correlated with outcome[5] and TIMI grade 2 has been associated with an outcome similar to that of an occluded artery.[6]

TIMI 0: Absence of complete antegrade flow

TIMI 1: Faint antegrade flow beyond the occlusion, incomplete filling of the distal coronary bed

TIMI 2: Partial reperfusion, delayed antegrade flow but with complete filling of the distal territory

TIMI 3: Normal flow, the distal coronary bed is completely filled

A more quantitative assessment is provided by the TIMI frame count (TFC), defined as the number of cine frames required for radiographic

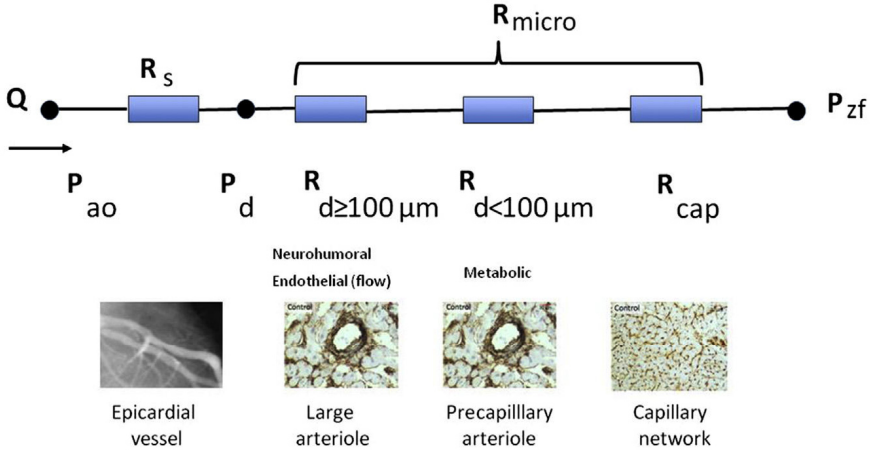

Fig. 1. Schematic representation of the coronary circulation as a resistive system. In the absence of a coronary stenosis, arteriolar tone constitutes the main seat of coronary resistance and is controlled by metabollic, myogenic, llow-dependent (enothelial) and neurogenic mechanisms. Microcirculatory dysfuntion may result from structural remodelling of arterioles or capillaries (rarefaction), dysregulation (paradoxical arteriolar vasoconstriction), hypersensitivity to vasoactive factor or adrenergic stimulation, and extravascular compression of collapsable vascular elements (capillaries). Pao, aortic pressure; Pd, pressure distal to the stenosis; Pzf, zero flow pressure; Q, coronary flow; Rcap, capillary resistance; Rmicro, microcirculatory resistance; Rd≥100mcm and Rd<100mcm, resistance of arterioles with diameters above and below 100mcm, respectively; Rs, stenosis resistance.

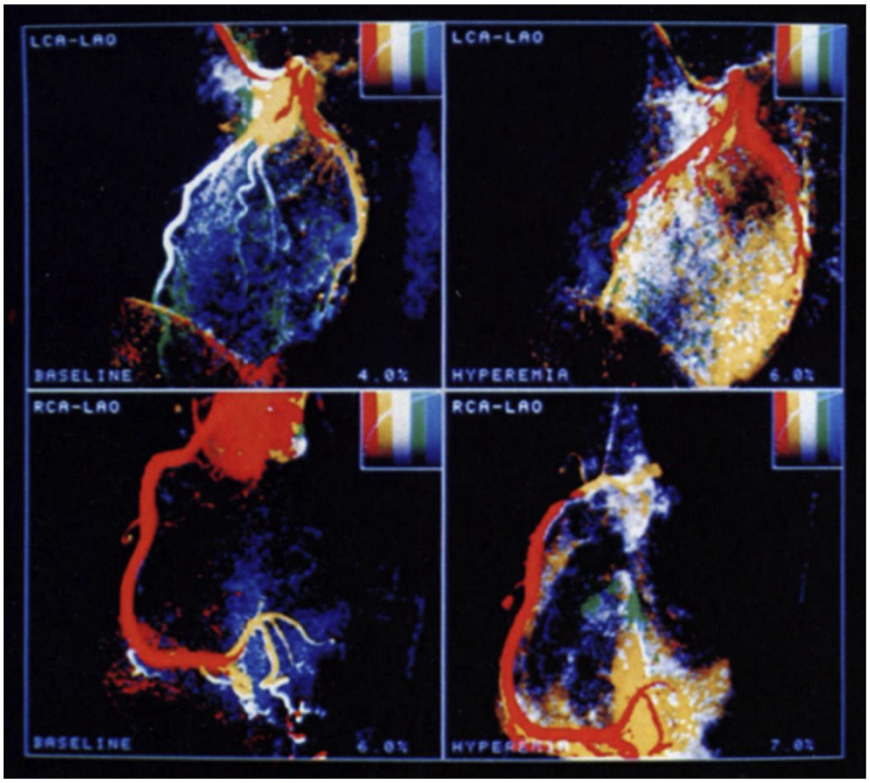

Fig. 2. Myocardial appearance time at angiography with digital enhancement. Left (*upper panels*) and right (*lower panels*) coronary systems are displayed at rest (*left panels*) and during hyperemia. (*From* Vogel R, LeFree M, Bates E, et al. Application of digital techniques to selective coronary arteriography: use of myocardial contrast appearance time to measure coronary flow reserve. Am Heart J 1984;107:153–64; with permission.)

contrast to reach a standardized distal coronary landmark in the culprit vessel, with length correction (CTFC) required for the left anterior descending artery (LAD).[7] A higher CTFC following thrombolysis is correlated with a higher CFR[8] as well as in-hospital and 30-day mortality.[9]

An attempt to angiographically visualize dye passing through the microcirculation can be made by establishing the degree of myocardial perfusion following angiographic injection with reasonable reproducibility and reliability. This is known as TIMI myocardial perfusion grading (TMPG). Following primary angioplasty, the degree of TPMG is correlated with mortality independent of the TFC.[10] Significantly, in patients with TIMI 3 flow following treatment of a myocardial infarction, an abnormal TPMG can be seen in up to two-thirds of patients and this has a significant impact on long-term mortality.[5,11] For example, in 924 subjects with TIMI 3 flow after a revascularized myocardial infarction a TPMG grade of 0 or 1 was associated with a higher mortality during the following 16 months.[12]

TMPG 0: Failure of dye to enter the microvasculature

TPMG 1: Dye enters slowly but fails to exit the microvasculature (still present at next injection)

TPMG 2: Delayed entry and exit from the microvasculature (persists after 3 cardiac cycles)

TPMG 3: Normal entry and exit from the microvasculature

However, although reasonably applicable, these direct-angiographic methods are relatively crude and subjective. Several studies have confirmed their insensitive nature. For example, a normal TFC can often be seen in patients with significant microvascular obstruction[13] or an abnormal CFR.[14] Therefore, more sophisticated techniques are required for an accurate assessment.

CORONARY FLOW RESERVE

CFR, the ratio of resting-to-hyperemic blood flow, was the one of earliest intravascular investigative tools implemented for assessing the coronary circulation. Of note, its first aim was to attempt to quantify coronary stenosis severity. Meticulous work by Gould and colleagues[15] demonstrated the effect of an increasing stenosis on resting and hyperemic flow rates. However, because of the variable influence of (particularly) the precapillary arterioles, it is difficult to use CFR to reliably assess coronary lesions. In contrast, controlling for epicardial resistance is relatively easy because in the absence of angiographically demonstrable disease the resistance of the large arteries of the heart is minimal and CFR provides information on the microvasculature alone.

Much discussion has gone into establishing the precise cut-off for an abnormal CFR, a value that has proved highly elusive. This is partly due to the continuous nature of the microcirculation in which, unlike coronary stenosis, no single value defines health versus disease. Additionally, almost all CFR-based studies have compared this value with other modalities that also provide a combined assessment of the macrovascular and microvascular circulation. Only a few, such as epicardial biopsy, focus on an alternative, microvascular-unique value.

Despite these issues, CFR as a tool for microcirculatory interrogation is one of the few intravascular investigative techniques that can be performed noninvasively through use of conventional echocardiography[16,17] (**Fig. 3**), myocardial contrast perfusion echocardiography,[18] or PET scanning.[19] This enhanced applicability allows for assessment of a much larger population than would be possible solely with invasive techniques and the conclusions that are drawn are also appropriate for any invasively obtained data.

CFR provides insights on the microcirculation in the postinfarct state. Following a revascularized myocardial infarction with TIMI 3 flow, a reduced CFR is associated with the presence of microvascular obstruction on MRI,[20] a feature in itself associated with a poorer prognosis[21] and infarct size.[22] Invasively measured CFR after primary percutaneous coronary intervention (PCI) therapy can predict the likelihood of ventricular recovery[23] and in-hospital mortality.[24]

In stable diabetic and prediabetic subjects, early microcirculatory abnormalities are recognizable as a low CFR.[25] An abnormal microcirculation has also been demonstrated with echocardiography-derived CFR in subjects with coronary syndrome X[16,26,27] and in subjects with multiple cardiovascular risk factors (hypertension, diabetes, obesity, impaired glucose tolerance) without overt coronary artery disease.[28] PET-derived CFR has been shown to be abnormal in hypertension,[29] diabetes,[30] hypercholesterolemia,[31] smoking,[32] left ventricular hypertrophy,[33] and aortic stenosis.[34]

Histologic comparisons have also been noted. There is a reasonable correlation between the presence of thin-cap fibroatheroma (on virtual histology–intravascular ultrasound) and an abnormal CFR, which indicates an important link between the pathogenetic processes of both epicardial and microvascular disease.[35] CFR is abnormally low in patients with idiopathic dilated cardiomyopathy[36] and correlates well with myocardial capillary density in this subgroup.[37]

CFR in stable patients also conveys important prognostic information. One of the largest prospective CFR studies was undertaken using transthoracic echocardiography of more than 4000 subjects in whom an abnormal LAD-CFR was an independent predictor of 4-year mortality.[38] PET has confirmed higher major adverse cardiac event rates in individuals with a low CFR over 10 years.[39] Alternatively, CFR from myocardial contrast perfusion echocardiography has been shown to be an independent predictor of myocardial infarction risk or death in 1252 subjects.[40]

In patients with coexisting intermediate coronary disease, the presence of an abnormal CFR is a significant risk factor for a major adverse cardiac event at 10 years, more so than an abnormal FFR, demonstrating the importance of both microvascular assessment and its involvement in outcome.[41] Similarly, in the Women's Ischemia Syndrome Evaluation (WISE) study, subjects with nonobstructive coronary disease but an abnormal coronary vasomotor response had a higher likelihood of events during the following 2 years.[42]

CFR can also quantify the microcirculatory impact within cardiomyopathic processes. In 129 subjects with a dilated cardiomyopathy of unknown cause and normal coronary arteries, a poor echocardiography-derived CFR is seen in up to 64% of subjects and is a predictor of adverse events (defined as worsening of heart failure symptoms or death).[43] An abnormal CFR is also a marker of poor outcome in hypertrophic cardiomyopathy (defined as left atrium dilatation, development of atrial fibrillation, hospitalization for unstable angina, implantable

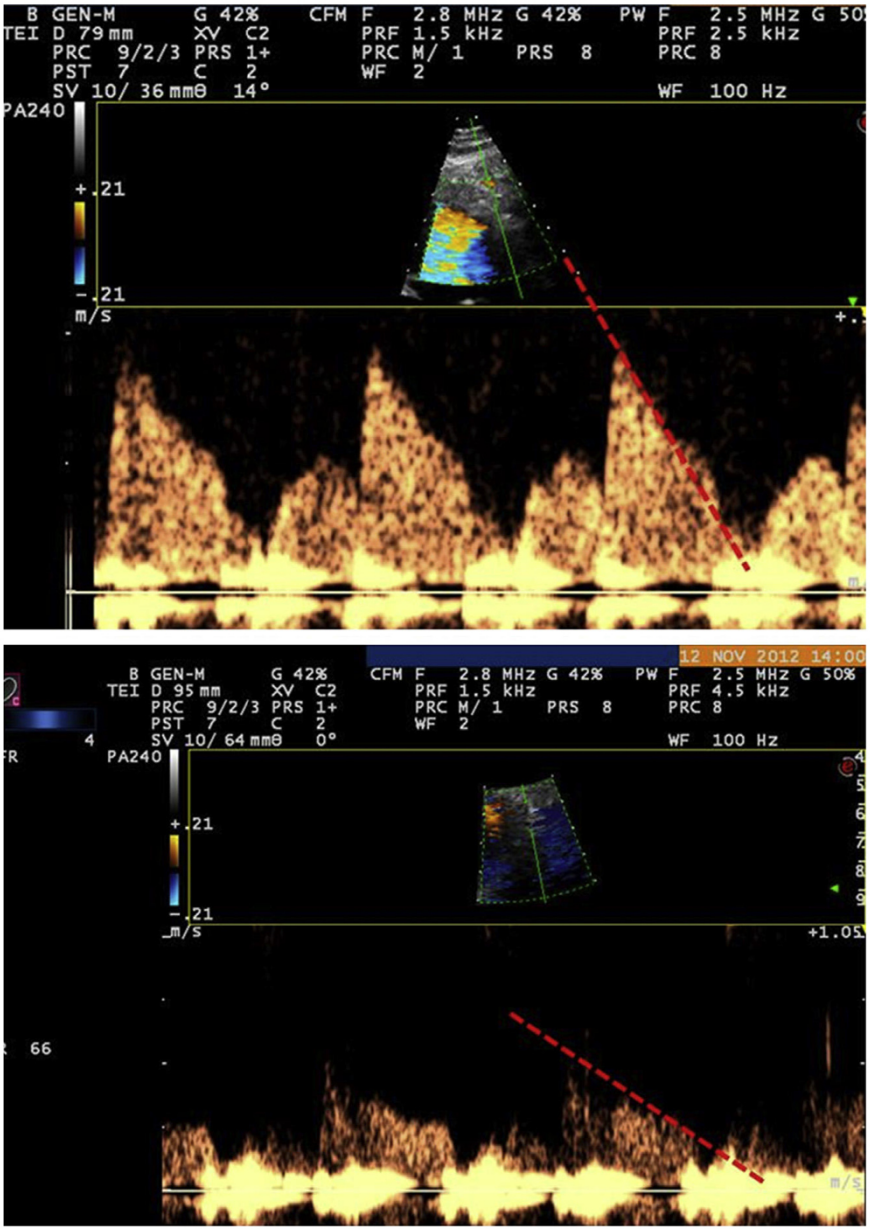

Fig. 3. Noninvasive coronary flow measured by transthoracic echocardiography with diastolic deceleration time marked in red. A more marked diastolic deceleration (*left panel*) is associated with poor microvascular function compared with the right panel. Alternatively or additionally, peripheral administration of a stressor agent would provide noninvasive CFR.

cardioverter defibrillator insertion, or permanent pacemaker insertion).[44]

However, despite the availability of CFR to interrogate the microcirculation, several caveats exist for its use. An increasing heart rate results in an higher resting coronary flow rate[45] but hyperemic rates are unchanged,[46,47] producing a relative reduction in CFR. Similarly, with volume expansion and a rise in pulmonary capillary wedge pressure, resting coronary flow rate is increased but hyperemic flow is unchanged, again resulting in a reduction in CFR.[47] There is also physiologic variability with a higher resting coronary flow rate seen in women[48] and with age.[49] Various pharmacologic agents also exert an effect on CFR independent of heart rate alterations.[50] Therefore, whereas pressure-derived indices strive for an accurate definition of peak hyperemia,[51] with flow-based measures it is the definition of rest that creates more difficulties undoubtedly contributing to the precision issues of CFR.[52]

RESTING CORONARY FLOW PATTERNS

Interest has also focused on resting coronary flow patterns as a marker of myocardial dysfunction. Initial work examined the Doppler flow profile in 42 subjects after angioplasty for acute myocardial infarction and the presence of no-reflow on myocardial contrast echocardiography. Although peak diastolic velocity was the same in subjects with and without no-reflow, diastolic deceleration (see Fig. 3) was significantly higher in the latter. Additionally, early systolic retrograde coronary flow was noted in these subjects.[53] This feature is thought to reflect capillary damage (rather than microembolization).[54]

Diastolic deceleration time and early systolic flow reversal also correlate with TIMI flow[55] and their presence confers prognostic information. In 169 subjects with a first myocardial infarction, these features were correlated with the development of congestive cardiac failure and in-hospital mortality.[56] Using noninvasive Doppler in 49 subjects with a successfully reperfused artery, the presence of systolic flow reversal was associated with a poor recovery of left ventricular function on transthoracic echocardiography.[57] Invasive Doppler flow profiles 4 days after acute myocardial infarction were also able to predict the degree of microvascular obstruction seen on MRI.[58] Moreover, additional use of intracoronary streptokinase at the time of primary angioplasty seems to result in a favorable improvement in diastolic deceleration time when measured invasively 2 days later.[59] In a prospective 4-year follow-up of 68 myocardial infarction subjects, these flow patterns were associated with outcome in terms of cardiac death, recurrent myocardial infarction, and congestive heart failure.[60]

INDEX OF MICROCIRCULATORY RESISTANCE

Through use of sensor-tipped wires, thermodilution has been shown to be a useful tool for estimating CFR[61] and has been validated as such in humans.[62] By including a combined distal pressure measurement with hyperemic thermodilution-derived transit time, the index of microcirculatory resistance (IMR) is calculated as the product of both (Fig. 4). This has been validated in animals[63] and humans[64] as a reliable measure of microvascular function independent of hemodynamic perturbations.

IMR has been used in stable and unstable settings to provide valuable prognostic and diagnostic information. In patients undergoing elective angioplasty, IMR was able to predict the likelihood of periprocedural myocardial infarction[65] and show, therefore, that the status of the microcirculation is involved in this risk. IMR has also been used to demonstrate the advantages of direct stenting, which resulted in a lower IMR than if lesion pretreatment with balloon dilatation was used[66] (a feature also demonstrated with CTFC[67]). Intracoronary angiotensin-converting enzyme (ACE)-inhibitors[68] or pretreatment with atorvastatin[69] for elective PCI also result in a more favorable post-angioplasty IMR, implying that these adjuvant therapies offer microcirculatory protection to any iatrogenic showers of atheroma.

IMR has an important role in unstable patients. In a study of 40 subjects who underwent primary angioplasty, IMR performed immediately afterward correlated well with viability on PET scans and left ventricular recovery at 6 months on echocardiography.[70] Similarly, in a group of 108 primary angioplasty subjects, IMR was correlated with early (2 days) and late (3 months) myocardial salvage at MRI (defined as the ratio of infarct to area at risk).[71] A second study of 57 STEMI subjects also showed a significant correlation between MRI-derived microvascular obstruction and periprocedural IMR.[72] IMR has been used to demonstrate the time course of microvascular recovery after myocardial infarction with a gradual improvement noted during the following 6 months in hyperemic transit time, CFR, and IMR.[20]

In the largest study of infarct-measured IMR, Fearon and colleagues[73] have shown that in 253 subjects an IMR of greater than 40 is an independent predictor of death or rehospitalization for heart failure during a 2.8 year follow-up. Finally, the shape of the thermodilution curve may provide further prognostic information; a wide bimodal shape predicts the likelihood of microvascular obstruction, heart failure rehospitalization, or death.[74]

IMR has a use in guiding adjuvant therapies at the time of primary angioplasty. Nicorandil, a nitric oxide donor, has a positive effect during myocardial infarction in which a consecutive reduction in microvascular resistance was seen with repeat administrations of intracoronary nicorandil. IMR also correlated well with TFC, myocardial blush grade, and peak creatine kinase.[75] Future research is planned to examine the effect of antiplatelet agents on microvascular function (as assessed by IMR) in acute coronary syndrome.[76]

In a study of 41 subjects randomized to receive intracoronary streptokinase at primary PCI, IMR was repeated after 2 days. Subjects in

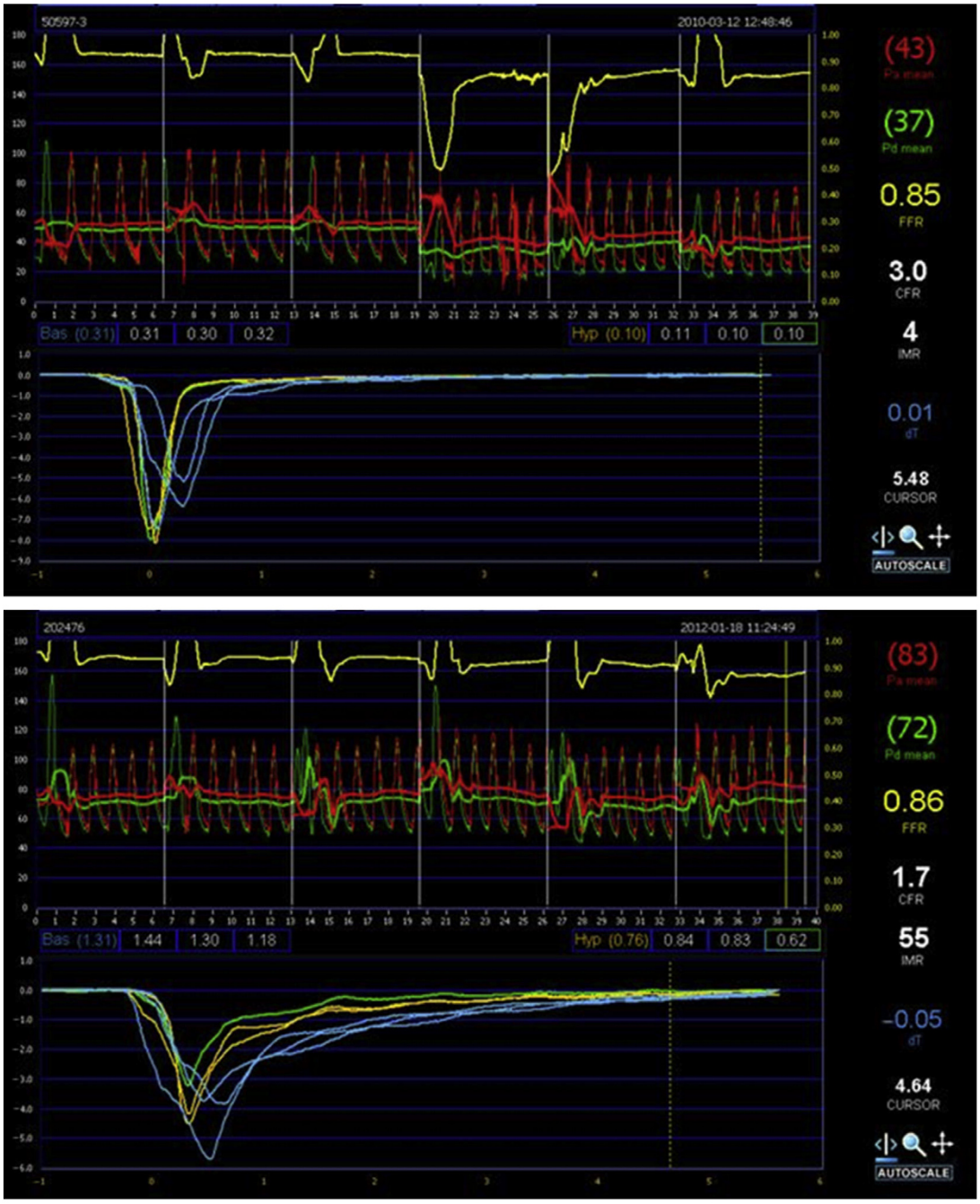

Fig. 4. The index of microvascular resistance in health and disease. The upper panel demonstrates a healthy vasculature with a low index of microcirculatory resistance (IMR) and high CFR. The lower panel demonstrates an unhealthy microvasculature with a high IMR and low CFR.

the streptokinase arm had significantly lower IMR levels (16 vs 32) although no differences were seen between these groups on echocardiography or PET scan.[59] A similar study of 36 STEMI subjects randomized to receive or not receive distal protection during angioplasty showed similar results; those who received distal protection the IMR also had significantly lower IMR levels (27 vs 37).[77]

The potential usefulness of IMR compared with CFR has been demonstrated in a study of 25 heart transplant subjects. Although CFR was

unchanged when measured after transplantation and at 1 year, FFR significantly worsened whereas IMR significantly improved. This implies that unfavorable epicardial changes occurred in conjunction with more favorable and opposing microcirculatory alterations. Because CFR is related to both epicardial and microvascular disease, if divergent changes occur, it is not able to distinguish these. Therefore, techniques that independently assess the microvasculature are much more informative in this setting.[78]

INSTANTANEOUS HYPEREMIC DIASTOLIC VELOCITY-PRESSURE SLOPE

Due to the inherent problems with CFR outlined previously, Mancini and colleagues[79] examined the relationship between pressure and flow during diastole under hyperemic conditions, measuring the pressure-volume slope during mid-diastole to late-diastole (Fig. 5) as a tool for stenosis assessment. In animal models, the instantaneous hyperemic diastolic velocity-pressure slope (IHDVPS) proved to be independent of hemodynamic variables, well-correlated with microsphere-derived coronary conductance (the inverse of resistance),[80] reproducible, and potentially more sensitive than CFR to epicardial stenosis.[81] It was also insensitive to changes in heart rate, contractility, and volume loading.[82]

Di Mario and colleagues[83] moved IHDVPS into the clinical environment in a study of 95 subjects, albeit still for epicardial stenosis severity assessment. Again, little effect was exerted by alteration in hemodynamic conditions and a reasonable correlation was obtained with stenosis severity, which was echoed by findings 2 years later.[84]

Subsequently, this technique was applied to assessing the microcirculation. Using a cohort of subjects who had undergone previous cardiac

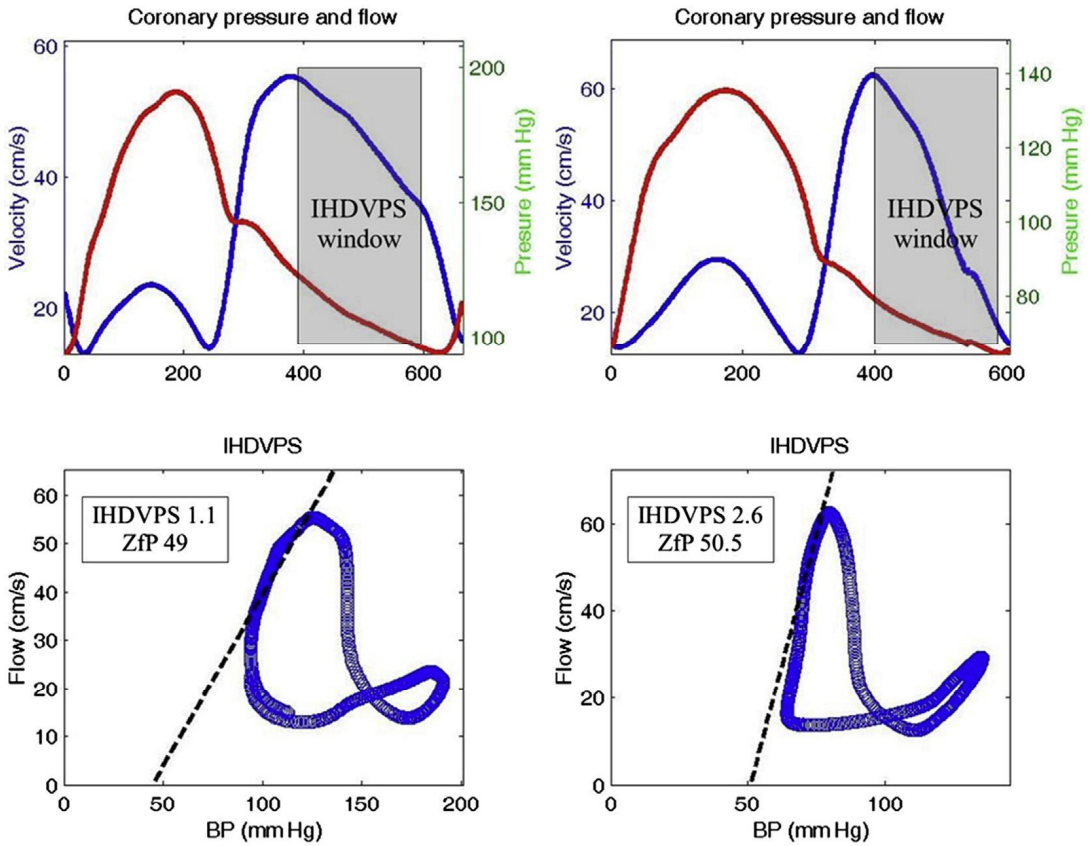

Fig. 5. Calculation of the coronary zero flow pressure and instantaneous hyperemic diastolic velocity-pressure slope (IHDVPS) in 2 patients (*right* and *left panels*). The slope of the diastolic relationship between pressure and flow provides a measure of conductance (the inverse of resistance). The x-intercept is the zero-flow pressure (ZFP). Both patients have a markedly elevated similar ZFP; however, the right panel displays a more favorable IHDVPS and thus lower resistance than the left panel. In the context of a myocardial infarction, both are likely to have an elevated left ventricular end-diastolic pressure; BP, blood pressure.

transplantation, Escaned and colleagues[85] performed simultaneous myocardial biopsy and intracoronary interrogation, thus linking physiologic indices with histologic findings. Notably, a good correlation was demonstrated with capillary density and arteriolar obliteration, although no link was demonstrated between histology and CFR. The same group also demonstrated a link between diastolic dysfunction in diabetic subjects and IHDVPS but not zero-flow pressure (ZFP).[86] Therefore, in the absence of coronary stenosis, IHDVPS seems to be a good tool for detecting microcirculatory changes.

The coronary pressure-volume loop also seems to be useful in acute myocardial infarction. In 27 subjects with anterior myocardial infarctions, both IHDVPS and ZFP correlated with myocardial viability on fluorodeoxyglucose (FDG)-PET scan (although IHDVPS did not quite reach significance).[87] Peri-infarct IHDVPS also correlates with the degree of myocardial salvage on technetium sestamibi (MIBI) scan,[88] the transmural extent of infarction on MRI,[89] and the likelihood of left ventricular remodeling.[90]

An elucidating study published by Van Herck and colleagues[91] used the model of myocardial infarction to demonstrate the dominant influence on ZFP. By comparing subjects with angina, non-Q wave infarction, and Q-wave infarction, a step-wise right-shift in the coronary flow relationship was demonstrated, a feature present in noninfarcted territory as well. Multivariate analysis showed that left ventricular end-diastolic pressure (LVEDP) was the most important determinant of ZFP. One caveat with the pressure-flow loop–derived ZFP was recognized by Di Mario and colleagues,[83] who suggested the relationship may become curvilinear at lower pressures, potentially hampering its use.

WAVE INTENSITY ANALYSIS

Initially developed as a tool in sound engineering and fluid dynamics, wave intensity analysis (WIA) has found a particular place in assessing the coronary microcirculation. It is derived from simultaneously acquired resting measures of pressure and flow. Unlike traditional Fourier-based interrogation of waveform data, it is calculated in the time-domain.[92] At its most basic level, net wave intensity (WI_{NET}) is constructed from the product of the first differential of pressure and flow:

$$WI_{NET} = dP \times dU$$

However, by incorporating the water-hammer equations and by standardizing by time it is able to provide the direction of origin of the separated force:

$$WI_{\pm} = 1/4\rho c \times (dP/dt \pm \rho c dU/dt)$$

ρc, where ρ is the density of blood and c is wave speed (itself calculated from a single measure of pressure and flow[93]). Coronary wave intensity is, therefore, able to separate out the proximal (aortic) and distal (myocardial) originating energy components that contribute to accelerate and decelerate coronary flow and provides an independent measure of the energy being exerted from the myocardium.

Although 6 waves have been identified per cardiac cycle, the dominant wave affecting coronary flow is the backward decompression wave (Fig. 6).[94] This wave was initially referred to as a suction wave, which reflects its mechanistic contribution because, as the microcirculation relaxes in diastole, a negative pressure gradient is created from the recoiling capillaries sucking blood into the microcirculation.

The microcirculation has been examined in various states using WIA. First, in left ventricular hypertrophy, a negative effect is seen on the backward decompression wave, reflecting the relative inefficiency of this state.[94] In severe aortic stenosis, despite the presence of significant left ventricular hypertrophy, the backward decompression wave is greatly increased due to the increased compression and relaxation necessary to expel blood through the stenotic aortic valve.[95] With pacing in severe aortic stenosis, the backward decompression wave decreases with an increased heart rate, reflecting a relative uncoupling of the normal mechanisms governing coronary blood flow and possibly accounting for angina in these patients. Importantly, this relationship returns to the physiologic norm immediately after transcatheter valve implantation.[95]

WIA has also been used in patients with coronary artery disease to investigate the phenomenon of warm-up angina in which an improvement in the cardiac-coronary coupling is seen with consecutive exertions.[96] The same group also used WIA to predict the likelihood of myocardial recovery on MRI after 3 months in 31 subjects who underwent revascularization following a non-STEMI.[97]

In biventricularly paced patients, optimization of the pacing regime (as determined by noninvasive blood pressure measurements) resulted in an increase in coronary blood flow velocity due to an increase in the backward decompression

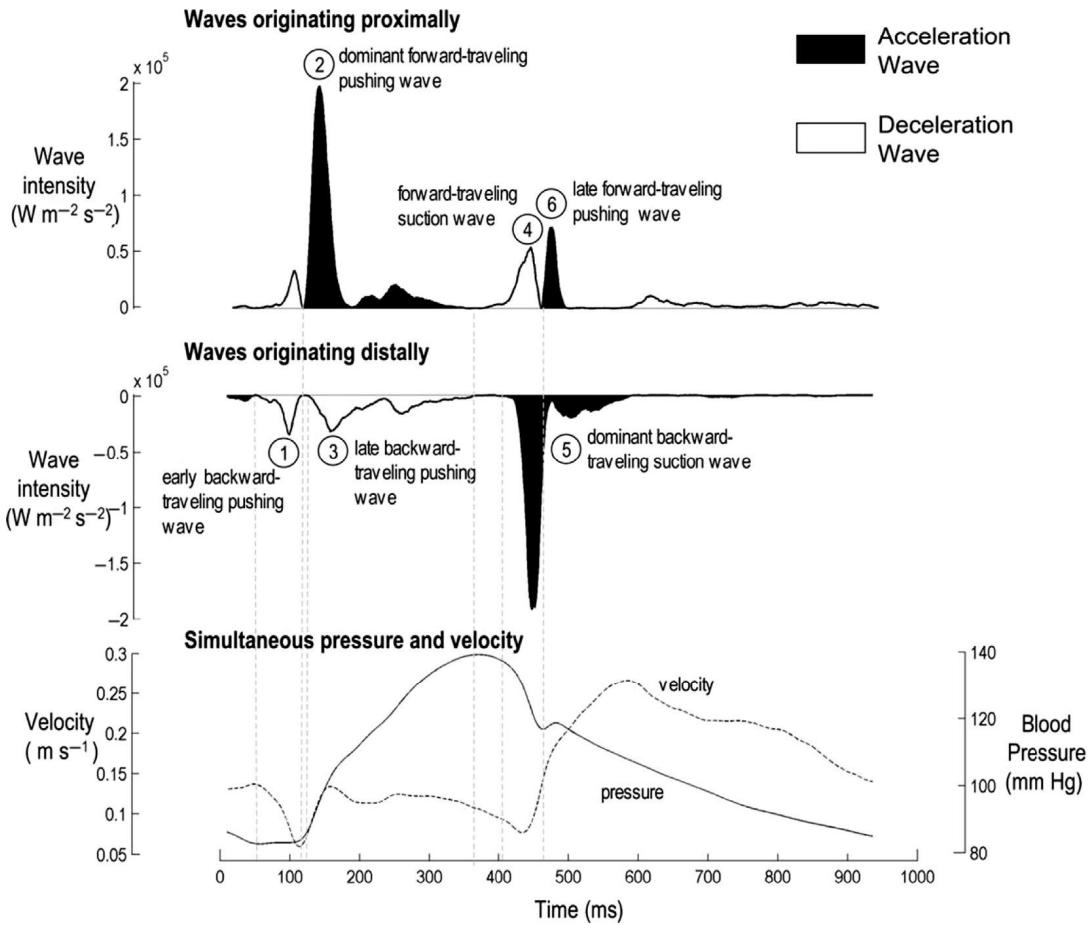

Fig. 6. Wave intensity profile in an unobstructed circumflex artery. Six waves are evident but the backward traveling suction or decompression wave (5) is responsible for coronary flow. This wave is generated by myocardial decompression at the onset of diastole. A pressure gradient is created from proximal to distal and this wave, therefore, provides a separated quantification of microvascular function. (*From* Davies JE, Whinnett ZI, Francis DP, et al. Evidence of a dominant backward-propagating "suction" wave responsible for diastolic coronary filling in humans, attenuated in left ventricular hypertrophy. Circulation 2006;113:1768–78; with permission.)

wave.[98] Finally, by documenting the wave-intensity profile of patients with moderate coronary lesions, a region of the cardiac cycle in which microvascular resistance is naturally low can be located and thus adenosine-free pressure-based assessment of coronary lesions can be performed.[99]

SUMMARY

The coronary microcirculation represents a vast network of conduits that cannot be directly visualized during angiography but whose role in channeling and regulating myocardial blood flow is paramount. Microcirculatory dysfunction is recognized in several clinical scenarios ranging from ischemia in the absence of epicardial stenosis, inherited cardiomyopathies, and acute myocardial infarction. Tools to investigate the microcirculation are not only essential for diagnostic purposes but also to guide treatment, particularly adjuvant therapies (such as thrombus aspiration or intracoronary pharmacotherapy) that may be required at the time of infarction. As such, the ability to assess the microcirculation using technology that can be applied at the time of angiography is essential to advancing the management of these conditions.

Although a basic understanding of the state of the microcirculation can be established from relatively direct angiographic markers, it is now obvious that, even in the presence of a normal blush grade or TIMI flow, significant abnormalities can still exist in the microcirculation. The resting coronary flow pattern is a more discriminatory tool and its use can predict outcome particularly by measuring the diastolic deceleration time and systolic flow reversal.

More sophisticated techniques rely on the induction of hyperemia to minimize microvascular tone. CFR measured in the absence of an epicardial stenosis allows direct assessment of the microcirculation. However, its variability with heart rate, volume status, age, and sex introduce several confounding factors. Despite this, CFR is one of the more widely applied and historically embedded techniques that can be replicated noninvasively. Therefore, it remains a potentially useful and applicable tool, particularly if ways of controlling for these confounding factors can be established.

To that end, IMR seems to be a promising thermodilution-based assessment technique involving simultaneous measures of pressure and thermodilution transit time with several documented advantages compared with CFR. However, it has some conceptual issues when coronary disease coexists owing to the presence of collateral flow. It requires either the measurement of coronary wedge pressure[100] or additional mathematical steps,[101] which add either complexity to the measurement or the potential to introduce error.

An alternate measure that combines hyperemic pressure and flow is IHDVPS, which has similar advantages compared with CFR due to its stability within varying hemodynamic states. However, achieving an optimal flow signal during hyperemia does require some skill and any pressure damping due to aggressive catheter engagement with the increased flow will have a marked effect. Additionally, there is concern about the use of the ZFP from the pressure-volume slope owing to the potential curvilinear relationship of pressure during low flow.[83]

WIA is able to assess the microcirculation in the resting state and incorporates measures of wave speed and blood density, as well as the pressure and flow waveforms. Although mathematically complex, when performed correctly it is able to provide independent information regarding microcirculatory function in the absence of a vasodilator. It has some disadvantages, particularly because, currently, no commercial software exists to provide a live measure and analysis is performed offline. Additionally, given its complex nature, there is a danger for error-exaggeration and some questions exist about how the data should be mathematically processed.[102] There is also some debate about the single-point equation for establishing wave speed, which, certainly during hyperemia, may not be as sound.[103]

In summary, as these techniques are applied and developed it is apparent that a single technique is unlikely to provide a complete comprehensive assessment of the microcirculation. Therefore, the future of intravascular assessment of the coronary microcirculation will most likely involve several complementary modalities ideally deployed simultaneously. As such, both wave-intensity analysis and IHDVPS can be gathered from a single pressure- and flow-tipped wire during periods of hyperemia and rest along with the more conventional measure of CFR. These may, therefore, integrate easily and synergistically. However, in the presence of significant epicardial disease, IMR also allows calculation of the FFR and this dual assessment tool may be more appropriate in this setting.

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2.3 The randomize clinical trial PRotective Effect on the coronary microcirculation of patients with DIabetes by Clopidogrel or Ticagrelor (PREDICT)

2.3.1. PREDICT: full English protocol and Spanish summary

PREDICT trial protocol (Nº EUDRACT: 2015-003621-33) was fully drafted by myself as Co-Principal Investigator and by Prof. Javier Escaned as Principal Investigator. Statistical planning was provided by Prof. Alicia Quiros (Statistical Departlment, University of Leon).

The protocol was granted and funded by the biopharmaceutical company AstraZeneca. The protocol is available at Clinical Trial website (www.clinicaltrials.gov; no. NCT02698618).

In this part the full PREDICT protocol is reported including study definition, physiological indices descriptions, statistical plan and outcome measurement.

Full English protocol

PRotective Effect on the coronary microcirculation of patients with DIabetes by Clopidogrel or Ticagrelor (PREDICT)

A randomized multicenter clinical trial using intracoronary multimodal physiology

Protocol version 1.3

May, 31st 2017

Coordinating center

Hospital Clínico San Carlos. Madrid, Spain

Promotor

Fundación Interhospitalaria de Investigación Cardiovascular. Madrid, Spain

INDEX OF CONTENTS

Data Collection

Clinical and Technical Procedures

- Patient History
- Physical Examination
- Electrocardiography (ECG)
- Blood Samples and Parameters Assessed
- Timing of Blood Draws
- Invasive Multimodal Physiology Assessment

Adverse Event Reporting

- Reporting of Adverse Events
- Duration of follow-up after Adverse Events
- Disease-related events or outcomes not qualifying as SAEs
- Clinical laboratory abnormalities and other abnormal test results
- Assessment of causality

Definitions

Access to Source Data/Documents

Ethical and Legal Considerations

- Promoter
- Ethical Considerations
- Independent Ethics Committee (IEC)
- Informed Consent
- Financing and Insurance
- Conduct of Study
- Personal Data and Data Protection
- Data Handling and Record Keeping
    - Completion of Case Report Forms
    - Archiving
    - Confidentiality
    - Responsibilities

Final Report and Publication Policy

Appendix

References

LIST OF ABBREVIATIONS

AUC: Area Under the Curve
BMI: Body Mass Index
CABG: Coronary Artery Bypass Graft Surgery
CBFV: coronary blood Flow Velocity
CFR: Coronary flow Reserve
CK-MB: Creatine Kinase Mioband
DAPT: Double Antiplatelet treatment
DM: Diabetes Mellitus status
ECG: 12-leads Electrocardiogram
ENT1: sodium-independent nucleoside transporter 1
FD-OCT: frequency-domain optical coherence tomography
FFR: Fractional Flow Reserve
FPG: fasting plasma glucose
GFR: Glomerular Filtration Rate
HDL: High density lipoprotein cholesterol
IEC: Independent Ethics Committee
IFG: impaired fasting glucose
IMR: index of microvascular resistance
IVUS: Intra Vascular Ultra Sound
LDL: Low density lipoprotein cholesterol
LVEF: Left Ventricular Ejection Fraction (%)
MACEs: Major Cardiovascular Events
NIRS: near infrared spectroscopy
OGTT: Oral Glucose Tolerance Test
PCI: Percutaneous Coronary Intervention
TCFA: thin-cap fibroatheroma
TIMI: Thrombolisis in Myocardial Infarction flow
VH-IVUS: virtual histology Intra Vascular Ultra Sound
WHO: World Health Organisation

STUDY SYNOPSIS

Title	PRotective Effect on the coronary microcirculation of patients with DIabetes by Clopidogrel or Ticagrelor
Study Rationale	1. Coronary plaque at high risk for distal embolization during PCI (like the one with TCFA) is more prevalent in patients with DM. This population is , therefore, at high risk to develop myocardial injury and microcirculation impairment subsequent to PCI. 2. Ticagrelor inhibits cellular uptake of adenosine, increasing the circulation levels of adenosine through the inhibition of its physiological clearance. Adenosine may protect the myocardium from both ischemic, and reperfusion injury via its potent vasodilatory effects and possibly by anti-inflammatory and antiplatelet properties. 3. Previous research from our group have identified a more profound effect of adenosine on microcirculatory resistance associated to obesity and diabetes and a higher myocardial protective effect of Ticagrelor during PCI might be expected in this high risk subgroup of patients.
Hypothesis	In patients with DM or pre-DM with ischemic heart disease undergoing PCI: 1. Ticagrelor is superior to Clopidogrel in providing microcirculatory protection during PCI procedures; 2. Ticagrelor is superior to Clopidogrel improving microcirculatory parameters also before PCI.
Objective	To investigate the protective effect of Ticagrelor on microcirculation during PCI in patients with DM or pre-DM.
Strategy	Baseline microcirculation assessment will be performed in eligible patients before randomization and allocation into Ticagrelor or Clopidogrel arms. After at least 48h of treatment, both pre and post-PCI microcirculation function will be assessed.
Study design	PREDICT is a multicenter, open-label, randomized clinical trial with two arms comparing Ticagrelor to Clopidogrel in terms of microcirculation protection in diabetic patients undergoing PCI.
Number of Subjects	50
Investigational Sites	– Hospital Clínico San Carlos, Madrid (Spain). Principal Investigator: Javier Escaned, MD, PhD; Co-principal Investigator: Enrico Cerrato, MD; C/Prof. Martín Lagos, s/n; 28040 Madrid. Phone: +34 913303438. – Hospital Universitario Marqués de Valdecilla, Santander (Spain). Site Principal Investigator: José María de la Torre, MD PhD; Av. Valdecilla, s/n; 39008 Santander, Cantabria. Phone: +34 942202520. – Hospital Galdakao, Bilbao (Spain). Site Principal Investigator: José Ramón Rumoroso, MD, PhD; Barrio Labeaga, s/n; 48960 Usansolo, Vizcaya. Phone: +34 944007000. – Hospital Universitario Puerta de Hierro. Investigador Principal local: Javier Goicolea Ruigomez; Calle Manuel de Falla, 1, 28222 Majadahonda, Madrid. Tel. 911 91 60 00

	– Hospital Universitario de Cabueñes. Investigador Principal local: Iñigo Lozano Martinez-Luengas. Calle Los Prados, 395, 33394 Gijón, Asturias. Teléfono: 985 18 50 00 (Patient recruitment will be competitive until reaching 50)
Primary Endpoints	1. Difference in microcirculatory resistance associated to PCI in DM or pre-DM patients treated with Ticagrelor or Clopidogrel (delta IMR-Post-PCI). 2. Difference in microcirculatory resistance associated to the initiation of Ticagrelor treatment in DM or pre-DM (delta IMR-Pre-PCI).
Secondary Endpoints	1. Myocardial necrosis associated to PCI damage, as assessed by cardiac markers in DM or pre-DM patients treated with Ticagrelor or Clopidogrel. 2. Absolute IMR value after PCI in DM or pre-DM patients treated with Ticagrelor or Clopidogrel. 3. Incidence (%) of severe microcirculatory impairment (IMR > 29) afer PCI in DM or pre-DM patients treated with Ticagrelor or Clopidogrel.
End of the study	At hospital discharge (all data required to test the primary and secondary endpoints will have been collected before patient's hospital discharge).
Target population, Inclusion and Exclusion criteria	The target population consists of patients with stable ischemic heart disease or stable coronary stenoses, with indication to FFR-guided revascularization and DM or pre-DM status referred for coronary angiography at the Hospital, presenting coronary stenoses in the coronary tree that are technically amenable for PCI, that can be investigated using pressure guidewire. Patients who are already on oral treatment with Clopidogrel are allowed to enter the protocol. In addition, it is anticipated that a proportion of patients will be treated on Aspirin alone as antiplatelet agent ("Clopidogrel naïve") allowing a comparison with patients on Clopidogrel in terms of delta IMR pre-PCI. INCLUSION CRITERIA: • Subject with Diabetes Mellitus Type II or pre-Diabetes Mellitus Type II status. • Subject must be older than 18 years. • Written informed consent available. • Patients with stable ischemic heart disease or stable coronary stenoses, with indication to FFR-guided revascularization, eligible for PCI. EXCLUSION CRITERIA: • Prior myocardial infarction in the territory of the target vessel. • Akinesia or dyskinesia in subtended myocardial segments. • • PCI target is a Chronic Total Occlusion • Target vessel is a saphenous vein graft or a surgical graft has been anastomosed to target vessel. • TIMI flow ≤ 1 prior to guide wire crossing. • Subject is not eligible for treatment with DES. • Bleeding disorders or chronic anticoagulant treatment. • Left main stenosis > 50%. • Coronary surgery deemed more beneficial for the patient than PCI. • Intolerance or contraindications to anti-platelet drugs.

	• Contraindications for adenosine administration. • Platelet count <75000 or >700000/mm^3. • Pregnant or breast feeding patient. • History of intracranial haemorrhage,	
Treatment	Experimental group Ticagrelor *Loading dose:* 180mg *Maintenance dose:* 90mg bid	Control group Clopidogrel *Loading dose:* 600mg *Maintenance dose:* 75mg die
Study Promotor	Fundación Interhospitalaria de Investigación Cardiovascular, Madrid (Spain)	
Principal Investigator	Javier Escaned, MD, PhD	
Co-principal Investigator	Enrico Cerrato, MD	
Steering Committee Members	Javier Goicolea MD, PhD, Iñigo Lozano, MD, PhD, José María de la Torre, MD, PhD; José Ramón Rumoso, MD, PhD; Mauro Echavarría-Pinto, MD; Antonio Fernández-Ortiz, MD, PhD; Carlos Macaya, MD, PhD	
Study core laboratory*	Hospital Clínico San Carlos, Cardiology Department; C/Prof. Martín Lagos, s/n; 28040 Madrid – Phone: +34 913303438. Co-Investigators/Core Laboratory: Christopher Broyd, MD, PhD; Mauro Echavarría-Pinto, MD; Nieves Gonzalo, MD, PhD; Alicia Quirós, PhD.	

* Study core laboratory for statistical analysis. During recruitment, all blood parameters will be determined at the local centre laboratory of each participating hospital.

SUMMARY

Diabetic patients still consistently perform worse than their non-diabetic counterparts especially in the setting of PCI. The abnormal coronary microcirculation along with the higher risk of distal embolization of particles released from the PCI target lesion constitutes the main cause of peri-procedural microcirculatory damage.

New antiplatelet agents, in particular Ticagrelor, might also play a protective role on microcirculation. Ticagrelor inhibits cellular uptake of adenosine, increasing the circulating levels of adenosine through the inhibition of its physiological clearance. Adenosine may protect the myocardium from both ischemic, and reperfusion injury via its potent vasodilatory effects and possibly by anti-inflammatory and antiplatelet properties.

Additionally previous research from our group have identified a more profound effect of adenosine on microcirculatory resistance associated to obesity and diabetes and a higher myocardial protective effect of Ticagrelor during PCI might be expected in this high risk subgroup of patients.

We plan to perform an original, prospective, randomized, controlled study to be carried out at Hospital Clínico San Carlos, Madrid, Spain - and other two centers - in order to investigate the protective effect of Ticagrelor on microcirculation during PCI in patient with Diabetes mellitus type II or in a pre-diabetic status.

INTRODUCTION

Microcirculatory damage during percutaneous coronary interventions.

Instrumentation of atheromatous vessels during percutaneous coronary interventions (PCI), such as balloon dilation or stent implantation, may lead to damage of the subtended microcirculation and myocardium. The most dramatic presentation of this phenomenon is the so-called no-reflow phenomenon(1), in which coronary flow is interrupted or severely impaired despite the absence of epicardial obstructions, causing acute EKG and haemodynamic disturbances. In most occasions, however, peri-procedural myocardial damage has much subtle presentations or is even clinically unnoticed. Distal embolization of particles released from the PCI target lesion constitutes the main cause of peri-procedural microcirculatory damage. In stable patients, micro-emboli have an origin in atheromatous plaque, mainly derived from cholesterol rich deposits named atheromatous gruel. Several studies(2) using virtual histology Intra Vascular Ultra Sound (VH-IVUS), frequency-domain optical coherence tomography (FD-OCT) near infrared spectroscopy (NIRS) have linked the occurrence of no-reflow phenomenon to PCI in cholesterol-rich plaques, mainly thin cap fibroatheromas. The same techniques have documented a higher prevalence of this type of plaques in patients with diabetes mellitus(3) (DM), who typically constitute a high-risk subset group of patients for PCI treatment. Patients with diabetes often have comorbidities and a greater burden of coronary artery disease(4) . However, despite correction for these factors, diabetic patients still consistently perform worse than their non-diabetic counterparts especially in the setting of PCI. The abnormal coronary microcirculation(5) along with the higher risk of peri-procedural microcirculatory damage in DM represent one of the harmful and still unmet issue potentially connected with a poor long-term outcome.

Several authors have proposed pharmacological strategies targeting the microcirculation to prevent peri-procedural damage. Since cardiac marker release is a vague indicator of microcirculatory damage (may occur as a result of small side branch occlusion unnoticed in angiography), the use of physiological techniques to measure modifications in microcirculatory resistance (IMR: index of microvascular resistance) has been advocated as a surrogate of microcirculatory damage. Previous studies conducted on DM patients demonstrated that IMR post PCI was higher in DM patients compared with non-DM ones as well as the severity of diabetic disease were significantly correlated with the occurrence of microcirculatory damage [IMRpost DM = 22.72 (13.35,42.91) vs. no DM = 13.9 (10.18,21.45), p = 0.02; Fasting blood sugar, HbA1c and IMR pre PCI were correlated with post PCI IMR value(6)].

New antiplatelet agents, in particular Ticagrelor, might also play a protective role on microcirculation, as discussed below.

Ticagrelor and adenosine metabolism

Beyond the antagonizing effect on P2Y12 receptor, several studies consistently showed that Ticagrelor inhibits the cellular uptake of adenosine. However to what extent this enhanced adenosine response contributes to its clinical profile is not yet documented. Intracellular adenosine is rapidly took up and metabolized in few seconds to inosine by adenosine deaminase or transformed into adenine nucleotides by adenosine kinase(7). Thus, it is possible to prolong its half-life by inhibition of its transport into cells. Ticagrelor delays cellular uptake of adenosine by inhibition of sodium-independent nucleoside transporter 1 (ENT1(8)) leading to a significant conserved adenosine level in human whole blood in vitro experiments. The final pathway is mediated by interaction with at least 4 different receptor subtypes (A1R, A2AR, A2BR, and A3R) which are coupled to stimulatory or inhibitory G proteins(9) carrying out a wide spectrum of biological effects and physiological responses.

Wittfeldt et al.(10) demonstrated for the first time an adenosine related mode of action for Ticagrelor in humans. In a double-blind, placebo-controlled, crossover study the coronary blood Flow Velocity (CBFV) was measured by using transthoracic Doppler echocardiography at rest after multiple stepwise adenosine infusions. Ticagrelor increases adenosine-induced physiological responses in term of enhancement of AUC for CBFV response versus adenosine dose compared with placebo. This increase correlated with Ticagrelor plasma concentrations and was mediated by adenosine receptors as demonstrated by the reversion of this effect after infusion of theophylline, a nonselective competitive adenosine receptor antagonist.

Protective effects of adenosine on myocardial injury associated to percutaneous interventions or acute coronary syndromes

Adenosine is routinely used in the catheterization laboratory for the treatment of no-reflow phenomenon during PCI, which constitutes an extreme manifestation of peri-procedural damage caused during PCI. No-reflow develops dramatically in response to vessel instrumentation, with contrast medium stagnation in epicardial arteries, persistent myocardial blush and, frequently, with accompanying ECG and haemodynamic changes. This complication is the result of plugging of the coronary microcirculation by downstream embolization of microthrombi or atheroma dislodged from the culprit lesion as a result of its manipulation during PCI(11). Reperfusion injury may also manifest as no-reflow phenomenon. Adenosine administration has demonstrated a protective effect preventing ischemia/reperfusion injury both humans(12) and in animal models(13).

The effects of adenosine on no-reflow have been investigated in numerous studies. A recent meta-analysis of 7 randomized clinical trials supported the benefit of intracoronary adenosine in terms of post-PCI ST-segment resolution and reduced residual ST-segment elevation, even if incidence of MACEs did not show differences between groups(14). Additionally the PROMISE trial recently showed a reduction in infarct size in post-PCI patients undergoing high-dose administration of intracoronary adenosine(15). All these effects could be related to the potent vasodilatory effects and potential anti-inflammatory and antiplatelet properties.

Microcirculatory and systemic responses to adenosine

Response after adenosine administration is heterogeneous and associated with relevant differences in clinical and intracoronary physiological characteristics. Based on an study performed with intracoronary multimodal physiology, we recently we reported that patients with diabetes mellitus type II (DMT2) or metabolic syndrome(16) (as shown by a high BMI) present enhanced responses to adenosine both at a systemic and coronary microcirculation levels (as shown by drop in systemic blood pressure and microcirculatory resistance). A possible explanation for this observation could be related to the heterogeneous impairment in adenosine receptor subtypes A1 reported in obese humans compared with non-obese(17).

This finding supports the hypothesis that the myocardial protective effect of Ticagrelor may be higher in patients with diabetes, pre-diabetes or metabolic syndrome. This is of particular importance, as PCI in patients with diabetes has been associated with higher peri-procedural events than in non-diabetic patients.

RATIONALE FOR THE PRESENT STUDY

The rationale for the study can be presented, on the grounds of all discussed in the introduction, as follows:

1. Coronary plaque at high risk for distal embolization during PCI (like the one with TCFA) is more prevalent in patient with DM. Thus, this population is at high risk to develop myocardial injury and microcirculation impairment subsequent to PCI.

2. Ticagrelor inhibits cellular uptake of adenosine, increasing the circulating levels of adenosine through the inhibition of its physiological clearance. Adenosine may protect the myocardium from both ischemic, and reperfusion injury via its potent vasodilatory effects and possibly by anti-inflammatory and antiplatelet properties.

3. Previous research from our group have identified a more profound effect of adenosine on microcirculatory resistance associated to obesity and diabetes and a higher myocardial protective effect of Ticagrelor during PCI might be expected in this high risk subgroup of patients.

STUDY HYPOTHESES

In patients with DM or pre-DM with ischemic heart disease undergoing PCI:

1. Ticagrelor is superior to Clopidogrel in providing microcirculatory protection during PCI procedures;

2. Ticagrelor is superior to Clopidogrel improving microcirculatory parameters also before PCI.

OBJECTIVE OF THE STUDY

To investigate the protective effect of Ticagrelor on microcirculation during PCI in patients with DM or pre-DM.

PRIMARY ENDPOINTS

1. Difference in microcirculatory resistance associated to PCI in DM or pre-DM patients treated with Ticagrelor or Clopidogrel (delta IMR-Post-PCI).

2. Difference in microcirculatory resistance associated to the initiation of Ticagrelor treatment in DM or pre-DM (delta IMR-Pre-PCI).

SECONDARY ENDPOINTS

1. Myocardial necrosis associated to PCI damage, as assessed by cardiac markers in DM or pre-DM patients treated with Ticagrelor or Clopidogrel.

2. Absolute IMR value after PCI in DM or pre-DM patients treated with Ticagrelor or Clopidogrel.

3. Incidence (%) of severe microcirculatory impairment (IMR > 29) after PCI in DM or pre-DM patients treated with Ticagrelor or Clopidogrel.

SUBSTUDIES

Prespecified subgroups of interest will be the subjects with obesity and subjects with prior myocardial infarction in another territory (different to the target coronary vessel).

DEFINITIONS

Index of microcirculatory resistance (IMR) will be calculated as mean distal coronary pressure multiplied by the hyperemic mean transit time. A coronary pressure/thermistor-tipped guidewire will be used as described below in detail (see the paragraph "Invasive Multimodal Physiology Assessment").

IMR at baseline will be defined as the value of IMR registered during the diagnostic angiogram.

IMR Pre-PCI will be defined as the value of IMR registered after randomization just before performing PCI+stenting.

IMR Post-PCI will be defined as the value of IMR registered just after performing PCI+stenting.

Delta IMR Post-PCI will be defined as the absolute difference in the IMR value associated to PCI ["Delta IMR Post-PCI" = (IMR value post-PCI) minus (IMR value pre-PCI)].

Delta IMR Pre-PCI will be defined as the absolute difference in the IMR value associated to PCI ["Delta IMR Pre-PCI" = (IMR value pre-PCI) minus (IMR value at baseline)].

Diabetes Mellitus Type II: according to the 2014 American Diabetes Association (18) patient will be considered to be diabetic if any of the following criteria is met:

1) haemoglobin A1C ≥ 6.5% The test should be performed in a laboratory using a method that is NGSP certified and standardized to the DCCT assay.* or

2) FPG ≥126 mg/dL (7.0 mmol/L). Fasting is de fi ned as no caloric intake for at least 8 h.* or

3) Two-hour plasma glucose ≥200 mg/dL (11.1 mmol/L) during an OGTT. The test should be performed as described by the World Health Organization, using a glucose load containing the equivalent of 75 g anhydrous glucose dissolved in water.* or

4) In a patient with classic symptoms of hyperglycemia or hyperglycemic crisis, a random plasma glucose 200 mg/dL (11.1 mmol/L).

*In the absence of unequivocal hyperglycemia, criteria 1–3 should be confirmed by repeat testing.

Pre-diabetes: according to American Diabetes Association(18) a patient will be considered to be in the pre-diabetic range if have:

a. an impaired fasting glucose (IFG) [fasting plasma glucose (FPG) levels 100 mg/dL (5.6 mmol/L) to 125 mg/dL (6.9 mmol/L)],

b. an impaired glucose tolerance (IGT) [2-h values in the oral glucose tolerance test (OGTT) of140 mg/dL (7.8 mmol/L) to 199 mg/dL(11.0 mmol/L)].

Individuals with IFG and/or IGT have been referred to as having prediabetes, indicating the relatively high risk for the future development of diabetes.

Obesity: will be defined as a Body Mass Index ≥30 kg/m 2 according to the international classifications of the World Health Organisation (WHO)(19).

PATIENT SELECTION, INCLUSION AND EXCLUSION CRITERIA AND WITHDRAWAL

The target population consists of patients with stable ischemic heart disease, on oral aspirin treatment (minimum 75mg daily) and DM or pre-DM status referred for coronary angiography at the Hospital, presenting coronary stenoses in the coronary tree that are technically amenable for PCI, that can be investigated using pressure guidewire.

Patients who are already on oral treatment with Clopidogrel 75mg/die are allowed to enter the protocol. According to randomization arm these patients will be assigned after baseline assessment of microcirculation to continue Clopidogrel 75mg/die treatment or to be switched to Ticagrelor 90 mg/bid. We considered to be acceptable including patients already on Clopidogrel considering that (i) no data about modification on microcirculation resistance subsequent to Clopidogrel administration have been ever reported (ii) Pretreatment with Clopidogrel may be considered in patients with high probability for significant coronary artery disease according to the current2014 ECS/EACTS guidelines on myocardial revascularization (19) and could reflect more the current clinical practice (iii) the reduction of index of microcirculatory resistance (IMR) from diagnostic angiogram to baseline pre-PCI assessment is defined as a secondary endpoint of the study. In addition, anticipating that a proportion of patients could be pre-treated with Clopidogrel allows a comparison with patients on aspirin alone as antiplatelet agent ("Clopidogrel naïve") in terms of delta IMR pre-PCI.

Inclusion criteria

- Subject with Diabetes Mellitus Type II or pre-Diabetes Mellitus Type II status.
- Subject must be older than 18 years.
- Written informed consent available.
- Patients with stable ischemic heart disease or stable coronary stenoses, with indication to FFR-guided revascularisation. eligible for PCI.

Exclusion criteria

- Prior myocardial infarction in the territory of the target coronary vessel.
- Akinesia or dyskinesia in subtended myocardial segments.
- PCI target is a Chronic Total Occlusion.
- Target vessel is a saphenous vein graft or a surgical graft has been anastomosed to target vessel.
- TIMI flow ≤ 1 prior to guide wire crossing.
- Subject is not eligible for treatment with DES.
- Bleeding disorders or chronic anticoagulant treatment.
- Left main stenosis > 50%.
- Coronary surgery deemed more beneficial for the patient than PCI.

- Intolerance or contraindications to anti-platelet drugs.
- Contraindications for adenosine administration.
- Platelet count <75000 or >700000/mm^3.
- Pregnant or breast feeding patient.
- History of intracranial hemorrhage.
- .

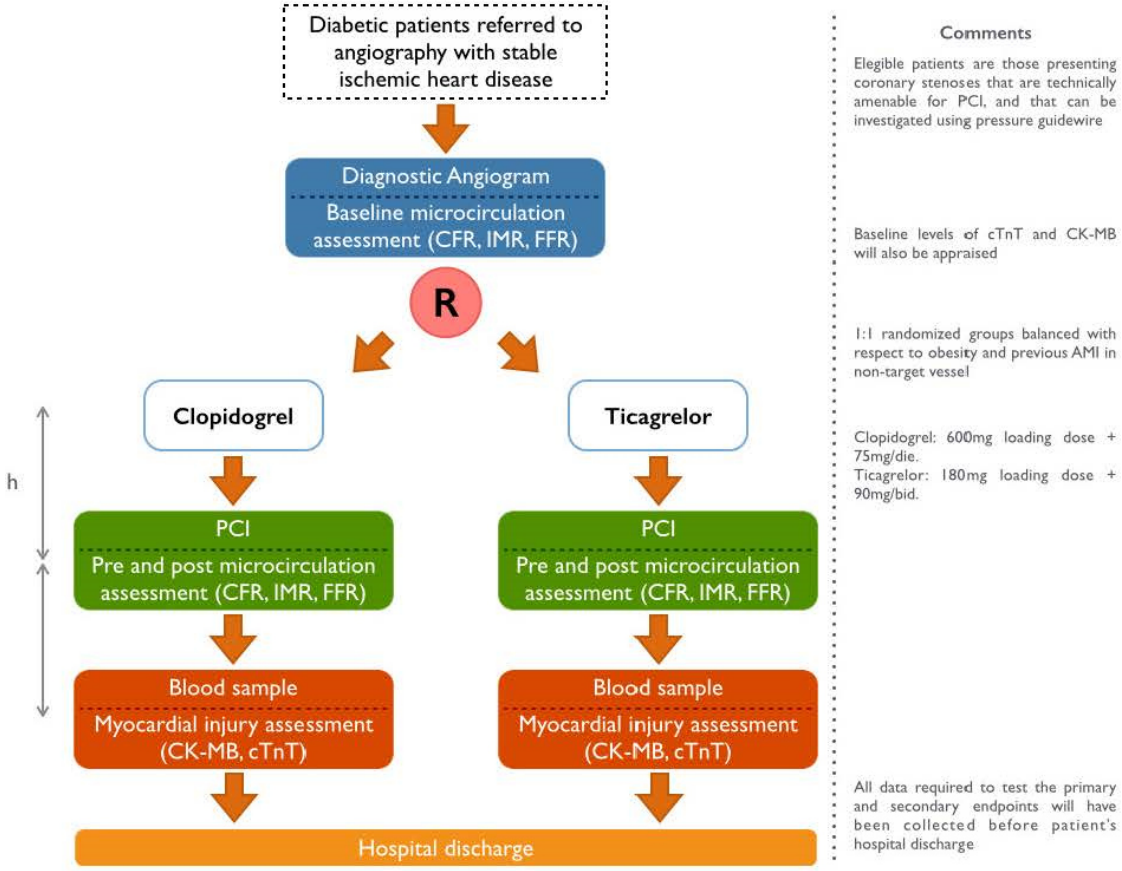
Withdrawals

Participants are free to withdraw from trial participation at their own request at any time without giving reasons for their decisions. Additionally, the main investigator of each site may withdraw study participants if continuation of the trial is deemed to be detrimental to the patient's well-being. Withdrawals will be documented in the case report form and in the patient's medical records with active follow-up for ongoing severe adverse events. Distinction will be made between patients who 'withdraw from the study' versus 'withdraw from the treatment' in order to preserve the ability to analyze endpoints for all participants who underwent randomization, allowing for the later possibility of intention-to-treat inferences. As detailed in the sample size calculation paragraph a low percentage of missing data due, for example, to withdrawals will be accepted.

TRIAL DESIGN

The design of the study will be that of a randomized clinical trial comparing two therapeutic strategies. We plan to perform an original, prospective, randomized, controlled study to be carried out at Hospital Clínico San Carlos, Madrid and in others 2 centers in Spain with proved experience in coronary percutaneous interventions and intracoronary physiologic assessment of microcirculation.

Study flowchart and protocol



Briefly, the study will be conducted as follows:

1. **At hospital admission:** all patients will undergo a complete physical examination, EKG and laboratory blood testing. Subjects will be investigated to confirm or eventually unmask existing diabetic or pre-diabetic status.
2. **Diagnostic angiogram**
   At the time of diagnostic catheterization of potentially eligible patients, physiological evaluation of stenosis severity will be performed using multimodal physiology assessment in order to evaluate the stenosis severity: CFR, IMR, and FFR will be measured according to methodology previously described{21–23}. Additionally, as routinely done, high-sensitivity cardiac troponin and kinase mioband (CK-MB) will be determined in a blood sample.
3. **Randomization**: patients addressed to percutaneous revascularization will be randomly assigned to receive either Clopidogrel or Ticagrelor before PCI. A loading dose of Ticagrelor 180mg followed by a dose of 90mg b.i.d. (during 48 hours) will be indicated to the experimental group; a loading dose of Clopidogrel 600mg followed by

a daily dose (during at least 48 hours) of 75mg will be administrated to the control patients.

4. **PCI procedure**
    a. Pre-PCI: multimodal physiological evaluation will be repeated.

    b. PCI: For all the patients undergoing PCI, the use of unfractioned heparin will be allowed at the time of PCI; UFH be administered with a target on ACT of 200-250 s. The PCI procedures will be performed by standard technique using only second generation Drug Eluting Stents. In all cases, balloon pre-dilatation will be performed before stent implantation in all cases using a semi-compliant balloon with a diameter lower than a 75% of the distal reference diameter of the vessel. (As recently demonstrated in a randomized controlled trial conventional stenting in comparison to direct stenting could affect the IMR value as a consequence of distal embolization of micro-emboli from the atheromatous plaque (direct stenting IMR 13 +/- 3, Vs predilatation+stenting IMR 24 +/- 14; $p < 0.01$(20) Post-dilation will be performed according to clinical practice although it will be not mandatory. All the characteristics related to PCI (materials and technique) will be recorded.

    c. Post-PCI: After stent implantation/s, multimodal physiological evaluation will be reperformed.

5. **In-hospital stay:** as routinely done, high-sensitivity cardiac troponin (I or T) and creatine kinase mioband (CK-MB) will be determined in blood samples taken after intervention. The peak values of troponin and CK-MB will be recorded. If significantly abnormal, serial measurements will be performed until a decline is noted.
6. **Before discharge:** the following examination will be performed:
    a. 12 lead ECG.
    b. Adverse events with related laboratory tests results, ECGs, details of the index procedure and any subsequent repeat coronary angiography and results of such, if applicable.
7. **In-hospital follow-up and data acquisition:** Major adverse cardiac events as well as any bleeding complication occurring during in-hospital stay will be properly recorded. All data required to test the primary and secondary endpoints will be collected before the hospital discharge of the patient.
8. **Antiplatelet treatment following PCI and patient's discharge:** At hospital discharge and termination of the participation of the patient in the study, double antiplatelet treatment regime (DAPT) will be decided by the responsible physician according to current recommendations, keeping in mind recommendations on DAPT switching if it is required (21, 22).

Informed consent

Informed consent will be obtained after diagnostic coronary angiography. Informed consent will be obtained by experienced clinical research staff in a non-coercive environment and in line with Good Clinical Practice guidelines.

Randomization

Patients will be randomly assigned to receive either Clopidogrel or Ticagrelor before PCI. Additionally the groups will be balanced according to obesity with the implementation of a dedicated randomization list. In this way two homogenous groups will be finally generated. The study arm will be determined by a computer-based randomization system integrated into the e-CRF.

TREATMENTS

Identity of products

Investigational product	**Dosage form and strength**	**Manufacturer**
Clopidogrel	75mg/day	Sanofi Winthrop Industrie
Ticagrelor (Brilinta)	90mg/bid	ASTRAZENECA

Doses and treatment regimens

Clopidogrel: loading dose of clopidogrel 600mg *per os* at the time of the randomization followed by 75 mg once a day *per os* according to current recommendations.

Ticagrelor: loading dose of ticagrelor 180 mg *per os* at the time of the randomization followed by ticagrelor 90 mg twice a day *per os* according to current recommendations.

Additional study drug

The following vasoactive agents will be administered during PCI procedure:

1. Adenosine (Adenoscan®)

Subjects will receive multiple intravenous adenosine infusions with the use of a stepwise dosing protocol (0, 50, 80, 110 and 140 µg/Kg/min) for a period of 2 minutes each to assess coronary vasomotion and flow.

2. Nitroglycerine (NTG) (Solinitrina®)

A nitroglycerin (NTG) intravenous bolus (200 µg) will be administered at the beginning of the physiologic study in both groups

3. Anticoagulation regimen

Procedural anticoagulation consisted of unfractionated heparin (100 IU/kg), with or bivalirudin monotherapy (0.75 mg/kg, followed by an infusion of 1.75 mg/kg/hr).

Banned drugs

Administration of any other drug (*per os* or intravenous) in addition to those specified above is banned during the multimodal physiological assessment study to avoid confounders except in case of emergency (clinical/hemodynamic instability) at the discretion of the responsible physician. Anyhow, any additional medication used will be recorded in case report form.

Drug supply

Ticagrelor drug will be supplied by AstraZeneca in the current commercial packages as a round, biconvex, yellow, film-coated tablet marked with a "90" above "T" on one side. Similarly, Clopidogrel drug will be supplied in the current pharmaceutical form as pink, round, biconvex film-coated tablets with a beveled edge, plain on both sides. Labelling of investigational medicinal drugs will be done according to applicable regulations (Directive 2003/94/CE, annex 13 GMP).

Storage

This medicinal product does not require any special storage

Disposition of unused supply of drug.

Any investigator site shall assure the return of all unused supplies of the investigational drug to the sponsor at the end of the study or in case of discontinuation from the study program.

Concomitant and post-study treatment(s

Any concomitant medication used during the study will be recorded in case report form. The data to be recorded will be the name of the drug, dose, and date of dosing as well as the reason or indication for administration. Other drugs, such as beta-blockers, ACE-inhibitors, ARA-II, Ca-antagonists, statins, etc will be administered, according to current guidelines. All patients will be under chronic ASA, according to current guidelines. Those patients not under chronic ASA treatment before the procedure will receive 300 mg iv bolus of ASA at the time of inclusion in the study. All patients will continue with their chronic treatment after the study as prescribed by their cardiologist.

Treatment Compliance

The loading doses of P2Y12 receptor blockers will be administered by clinic personnel, thus ensuring treatment compliance during hospitalization. Should the patient be discharged in the interim between diagnostic angiography and PCI, counting of the tablets provided to the patient to ensure treatment compliance will be performed and documented in the eCRF and

source documents. In case of lack of treatment compliance, PCI will be postponed until the minimum treatment period with P2Y12 receptors has been covered.

Procedures for discontinuation of a subject from investigational product

Discontinuation of therapy will be at the discretion of the investigator or the patient. In case of a clinical or laboratory adverse event requiring an interruption in the study medication, the reasons for discontinuing treatment will be recorded both in the medical records and the case report form and the investigator will start the treatment judged appropriate in his opinion.

Potential adverse events related to drugs

See detailed paragraph in "Adverse Event Reporting", page 26.

SAMPLE SIZE AND STATISTICAL ANALYSIS

As no studies are available specifically reporting on the impact of Ticagrelor on microvascular function as opposed to Clopidogrel, we based our sample size calculation on a previous study (23) showing that the intracoronary administration of Nicorandil after PCI resulted in a difference of 10 units in deltaIMR with respect to the control group. Assuming a difference of 10 in deltaIMR in the experimental vs. control group, and a standard deviation of 10, a total of at least 20 patients per group would be needed to achieve an 80% power at a 2-sided alpha of 0.025, thus accounting for the multiple primary endpoint design with a Bonferroni correction. Therefore, we aim to enroll 25 patients per group taking into account a potential percentage of missing data / major protocol violation due to clinical reasons (for example: clinical instability of patient between index and PCI procedure leading to urgent revascularization before completion of the protocol).

Continuous variables will be expressed as mean +/- SD or as median (Q1-Q3), as appropriate. Categorical variables will be reported as frequencies and percentages. Normal distribution will be tested with the Shapiro-Wilk test. Comparisons between continuous variables will be performed using the (paired or unpaired) Student-t test or Mann-Whitney U test. The IMR at baseline, before PCI, and after PCI will be compared with an ANOVA for repeated measures or with the Kruskal-Wallis test, as appropriate. Comparisons between categorical variables will be evaluated using the Fisher exact test or the Pearson chi-square test, as appropriate. Correlations between continuous variables will be assessed using the Spearman rank correlation test. A 2-way ANOVA for repeated measures will be used to detect changes in IMR levels over time in the two study groups. Statistical analyses will be performed using R software version 3.1.1 and p-values <0.05 (2-tailed) will be considered significant.

STUDY DURATION

The enrollment period has an expected duration of 12 months. In addition, a preliminary analysis after 6 months shall be obtained to provide material for an initial study presentation.

The overall duration of the study will correspond to the enrollment period plus 1-3 months in which the core lab will analyze the data in order to prepare the final report.
According to the design of the study a patient will complete the protocol in 3-5 days from the time of enrollment. Briefly:

1. Enrollment and diagnostic procedure (Time zero)
2. Randomization and treatment with study drug (at least 48 hours)
3. PCI procedure
4. Discharge (at least 24 hours after PCI)

Drop-out criteria

1. Withdrawal of patient consent: Informed patient consent is voluntary and required from all patients. The patient can withdraw her or his consent at any time. If a patient withdraws her or his consent, the investigator should try to ascertain the reasons of withdrawal while fully respecting patient's rights. If the health status of the patient does not allow further participation in the study the investigator will decide on early study termination. An early study termination or withdrawal will not affect the patient's future medical care in any way.
2. Regular termination of the study: Patients will terminate their study participation at the time of hospital discharge.
3. Death: The investigator should notify any patient death during the investigation. In case of death, the investigator should fill in all the related eCRF (SA(D)E Form, Death Form and Study Termination Form).

DATA COLLECTION

A dedicated electronic Case Report Form (eCRF) will be designed and managed by one of the investigators (Enrico Cerrato, MD, Hospital Clínico San Carlos, Madrid, Spain) and hosted in the collaborative CardioGroup.org platform. All data will be stored securely and confidentiality.

- Apendix 1 lists all the clinical, angiographic and PCI procedural variables that will be recorded.
- Apendix 2 lists all the physiology data related to intracoronary assessment at different stages of the study.

CLINICAL AND TECHNICAL PROCEDURES

	Enrollment, diagnostic procedure and randomization	PCI procedure	Discharge
Patient History			
Physical Examination			
Electrocardiography (ECG)			
Blood Samples and Parameters Assessed			
Invasive Multimodal Physiology Assessment			
PCI with stenting			

Table: clinical and technical procedure timetable

Patient History

The patient's history must be taken according to the schedule as derived from the CRF with particular focus on major adverse cardiac events.

Physical Examination

The aim of the physical examination is to assess angina status, clinical history, and baseline medication. A complete physical examination of the patient must be performed before enrollment, after the procedure, and at any time when scheduled or unscheduled follow-up will be performed.

Electrocardiography (ECG)

All patients will undergo pre-intervention and post-intervention 12-lead ECG to detect procedure related ischemic changes (Q-wave myocardial infarction: appearance of a new pathological Q-wave). Calibration marks or clear notations should be inscribed on each ECG tracing to enable the interpreter to determine the paper speed and gain settings used in recording. Standard settings of a paper speed of 25 or 50 mm per sec according to the local routine, and a calibration of 10 mm per mV should be used unless required by technical reasons and indicated on the tracing.

Blood Samples and Parameters Assessed

Routine laboratory parameters must be assessed prior to the intervention as a part of the screening procedure in order to verify the enrolment criteria. They include serum creatinine, CK, blood cell count,cardiac markers (CK-MB -creatinine phosphokinase myocardial bound and troponin).

The peak values of troponin and CK-MB will be recorded following the procedure. If abnormal, erial measurements must be performed until a decline is noted.

Parameters to be assessed before the procedure/randomization. . If some of the following is not available at the time of procedure/randomization, they can be collected during the hospitalization as routine or even within 12 month before the hospitalization (In the absence of significant changes in the state of health considering that the present study is enrolling patients presenting with stable ischemic heart disease)

- Cardiac enzymes: CK-MB and troponin.
- Hematology : Hemoglobin, hematocrit, WBC, RBC, thrombocytes.

Evaluation of renal function: Serum creatinine (GFR should be calculated according to Cockroft-Gould),

Parameters to be assessed after any catheterization procedure:

- Cardiac enzymes: CK-MB and troponin.
- Hematology: Hemoglobin, hematocrit, WBC, RBC, thrombocytes.

- Evaluation of renal function: Serum creatinine (GFR should be calculated according to Cockroft-Gould), sodium, potassium, urea.

Timing of Blood Draws

The basic assessment is done before the index procedure or at time of randomization.. If some blood samples is not available at the time of procedure/randomization, they can be collected during the hospitalization as routine or even within 12 month before the hospitalization (In the absence of significant changes in the state of health considering that the present study is enrolling patients presenting with stable ischemic heart disease)

In case of significant elevation of cardiac enzymes, increase in serum creatinine, or drop in hemoglobin, a repeat evaluation should be performed until the peak of change in parameters can be assessed. Blood analysis will be repeated after any catheterization procedure. All blood parameters will be determined at the local centre laboratory of each participating hospital.

Invasive Multimodal Physiology Assessment

An intracoronary pressure and temperature sensor-tipped guidewire (St. Jude Medical) will be used to measure distal coronary pressure and to derive thermodilution curves as previously described (24). Three thermodilution curves will be obtained from a hand-held, 3-ml rapid (<0.25s) injection of room temperature saline at baseline and during maximal hyperemia, which will be achieved by infusion of 140 µg/kg per minute of adenosine via the femoral vein. Mean transit time (Tmn) at baseline and during maximal hyperemia will be derived from the thermodilution curves. Simultaneous recordings of mean aortic pressure (guiding catheter, Pa) and mean distal coronary pressure (distal pressure sensor, Pd) also will be obtained at baseline and during maximal hyperemia. The CFR will be calculated from the ratio of hyperemic to baseline Tmn. The IMR will be calculated using the following equation: IMR = PaxTmn[(Pd-Pw)/(Pa-Pw)], where Pw is the coronary wedge pressure. Pw will be measured as the distal coronary pressure (from the distal pressure and temperature sensor) during complete balloon occlusion of the vessel obtained during PCI. The FFR will be calculated from the ratio of distal to proximal pressures at maximal hyperemia.

ADVERSE EVENT REPORTING

Reporting of Adverse Events

The investigator is responsible for reporting of safety.

Definition of Adverse Events

An adverse event (AE) is the development of an undesirable medical condition or the deterioration of a pre-existing medical condition following or during exposure to a pharmaceutical product, whether or not considered causally related to the product. An undesirable medical condition can be symptoms (eg, nausea, chest pain), signs (eg, tachycardia, enlarged liver) or the abnormal results of an investigation (eg, laboratory findings, ECG). In clinical studies, an AE can include an undesirable medical condition occurring at any

time, including run-in or washout periods, even if no study treatment has been administered. The term AE is used to include both serious and non-serious AEs.

Definitions of Serious Adverse Events

A serious adverse event is an AE occurring during any study phase (ie, run-in, treatment, washout, follow-up), that fulfils one or more of the following criteria:

- Results in death.
- Is immediately life-threatening.
- Requires in-patient hospitalization or prolongation of existing hospitalization.
- Results in persistent or significant disability/incapacity or substantial disruption of the ability to conduct normal life functions.
- Is a congenital abnormality or birth defect.
- Is an important medical event that may jeopardize the patient or may require medical intervention to prevent one of the outcomes listed above.

The Investigator is encouraged to report promptly all adverse events, preferably, no later than 24 hours after the event or after being informed about the event.

At each evaluation, the investigator will determine whether any adverse events (AEs) have occurred. For the purpose of this study, an AE is any undesirable clinical occurrence in a subject that can be attributed to the procedure, or medications required by this protocol. In addition, all MACE events, bleedings and deaths will be recorded as AEs.

Duration of follow-up after Adverse Events

All adverse events must be followed until resolution or until a stable clinical endpoint is reached.

Disease-related events or outcomes not qualifying as SAEs

An event which is part of the natural course of the disease under study does not need to be reported as an SAE. However, if the event is greater than that which would normally be expected for the subject, or if the investigator considers that there was a causal relationship between treatment with randomized therapy or protocol design/procedures and the event, then this must be reported as a SAE.

Clinical laboratory abnormalities and other abnormal test results

Abnormal laboratory findings or other abnormal assessments that are judged by the investigator as clinically significant will be recorded as AEs or SAEs if they meet the definition of an AE, or SAE. Clinically significant abnormal laboratory findings or other abnormal assessments that are detected during the study or are present at baseline and significantly worsen following the start of the study will be reported as AEs or SAEs.

However, clinically significant abnormal laboratory findings or other abnormal assessments that are associated with the disease being studied, unless judged by the investigator as more severe than expected for the subject's condition, or that are present or detected at the start of the study and do not worsen, will not be reported as AEs or SAEs.

Assessment of causality

The investigator is obligated to assess the relationship between a study procedure and the occurrence of each AE/SAE. The investigator will use clinical judgment to determine the relationship. Alternative causes, such as natural history of the underlying diseases, concomitant therapy, other risk factors, and the temporal relationship of the event to the study procedure will be considered and investigated.

DEFINITIONS

MACE: Major adverse cardiac events are defined as cardiac death, non-fatal myocardial infarction, and ischemia driven premature target lesion revascularization during hospitalisation.

PCI-related myocardial infarction (type 4a): is defined as post- procedural increase in Troponin more than 5 times the 99th percentile of the upper reference limit for patients with baseline negative myocardial necrosis markers consistent with the joint European Society of Cardiology/American College of Cardiology Foundation/American Heart Association/World Heart Federation Task Force for Universal Definition of Myocardial Infarction consensus statement on the definition of myocardial infarction for clinical trials on coronary intervention. PCI-related myocardial infarction was also reported in the study results as increase in CK-MB more than 3 times the 99th percentile of the upper reference limit.

Death: any cause death.

Cardiac death: any death without a non-cardiac cause.

Repeat revascularization: classified as target lesion re-interventions (TLR) inside the implanted stent or within 5 mm proximally or distally or repeated interventions in the same vessel (TVR) by percutaneous coronary interventions (PCI) or by coronary artery bypass graft surgery.

Stent thrombosis (ST) will be classified as "acute"- within 24 hours from the procedure, "sub-acute" up to 30 days, "late" from 30 days till 1 year and "very late" after 1 year after index procedure.

Thrombosis will be classified as definite, probable and possible according to the definition of Academic Research Consortium.

ST will be defined as the occurrence of one of the following events:

1. Angiographic documentation of complete or partial stent occlusion and target vessel related acute clinical ischemic event.
2. Autopsy documentation of complete or partial thrombotic stent occlusion
3. Myocardial infarction in the distribution of the stented vessel.

We will separately evaluate the incidence of possible ST by including all unexplained death after 30 days.

Major bleeding defined as the cumulative occurrence of intracranial or intraocular bleeding, hemorrhage at the vascular access site requiring intervention, a reduction in hemoglobin levels of at least 5 grams per deciliter, reoperation for bleeding or transfusion of a blood product (at least 2 units). All other bleeding events were considered as minor (i.e. epistaxis, blood traces in the stool, etc.

Reporting

Reporting requirements will comply with all EU safety reporting requirements as detailed in "Directive 2001/20/EC of the European Parliament and of the council of 4 April 2001 on the approximation of the laws, regulations and administrative provisions of the Member States relating to the implementation of good clinical practice in the conduct of clinical trials on medicinal products for human use" and the associated guideline CT-3.

The Sponsor or its designee is responsible for reporting relevant SAEs to the Competent Authority, and Ethic committees, in accordance with International Conference on Harmonization (ICH) guidelines, European Clinical Trials Directive (Directive 2001/20/EC), and/or local regulatory requirements.

The Sponsor or its designee is responsible for reporting unexpected fatal or life-threatening events associated with the use of the study drug to the competent authorities and Ethic Committees within 7 calendar days after being notified of the event. The Sponsor or its designee will report other relevant SAEs associated with the use of the study medication to the appropriate competent authorities and Ethics Committees (ECs) by a written safety report within 15 calendar days of notification, following the local legislation.

The sponsor is required to notify AstraZeneca of all SUSARs, at the same time that the reports are sent to the local Regulatory Authority. Reports should be sent to AstraZeneca on a CIOMS form. In addition, the Sponsor must provide AstraZeneca with a quarterly report of all other SAEs that did not qualify for expedited reporting to the local Regulatory Authority.
Astrazeneca contact:

- Patientsafety.spain@astrazeneca.com
- Tel: 900 200 444
- Fax: 91 301 91 04

Variables

The following variables should be collect for each AE:

- AE (verbatim)
- The date <<and time>> when the AE started and stopped
- Whether the AE is serious or not
- Investigator causality rating against the Investigational Product (yes or no)
- Action taken with regard to investigational product
- <<Select the appropriate as required: AE caused subject's withdrawal from study (yes or no)>>
- Outcome

In addition, the following variables should be collected for SAEs:

- Date AE met criteria for serious AE
- Date Investigator became aware of serious AE
- AE is serious due to...
- Date of hospitalisation
- Date of discharge
- Probable cause of death
- Date of death
- Autopsy performed
- Causality assessment in relation to Study procedure(s)
- Description of AE.

POTENTIAL ADVERSE EVENTS

1.Side effect associated with study drugs:

General Risk of Bleeding: drugs that inhibit platelet function including Clopidogrel and Ticagrelor increase the risk of bleeding. Ticagrelor increased the overall risk of bleeding (Major + Minor) to a somewhat greater extent than did clopidogrel. The increase was seen for non-CABG-related bleeding, but not for CABG (Coronary Artery Bypass Graft Surgery)-related bleeding. Fatal and life-threatening bleeding rates were not increased.

In general, risk factors for bleeding include older age, a history of bleeding disorders, performance of percutaneous invasive procedures, and concomitant use of medications that increase the risk of bleeding (e.g., anticoagulant and fibrinolytic therapy, higher doses of aspirin, and chronic nonsteroidal anti-inflammatory drugs.

The following table reported annualized rate of Non-CABG related bleeding reported in PLATO trial (25)

	Ticagrelor (N=9235)	Clopidogrel (N = 9186)
Total (Major + Minor)	8.7	7
Major	4.5	3.8
Fatal/Life-threatening	2.1	1.9
Fatal	0.2	0.2
Intracranial (Fatal/Life-threatening)	0.3	0.2

Common Adverse Events A variety of non-hemorrhagic adverse events occurred in PLATO trial (25) at rates of 3% or more. These are shown in the table below. In the absence of a placebo control, whether these are drug related cannot be determined in most cases, except where they are more common on ticagrelor or clearly related to the drug's pharmacologic effect (dyspnea).

	Ticagrelor (N=9235)	Clopidogrel (N = 9186)
Dyspnea (%)	13.8	7.8
Headache (%)	6.5	5.8
Cough (%)	4.9	4.6
Dizziness (%)	4.5	3.9
Nausea (%)	4.3	3.8
Hypertension (%)	3.8	4
Non-Cardiac chest pain (%)	3.7	3.3
Diarrhea (%)	3.7	3.3
Back pain (%)	3.6	3.3
Fatigue (%)	3.2	3.2
Gynecomastia	0.23	0.05
Gout	0.6	0.6

Bradycardia:In clinical studies Ticagrelor has been shown to increase the occurrence of Holter-detected bradyarrhythmias (including ventricular pauses). PLATO excluded patients at increased risk of bradycardic events (e.g., patients who have sick sinus syndrome, 2nd or 3rd degree AV block, or bradycardic-related syncope and not protected with a pacemaker). In PLATO, syncope, pre-syncope and loss of consciousness were reported by 1.7% and 1.5% of ticagrelor and clopidogrel patients, respectively. In a Holter substudy of about 3000 patients in ticagrelor, more patients had ventricular pauses with Ticagrelor (6.0%) than with clopidogrel (3.5%) in the acute phase; rates were 2.2% and 1.6% respectively after 1 month.

Drugs interactions: concomitant use of strong inhibitors of CYP3A (e.g., ketoconazole, itraconazole, voriconazole, clarithromycin, nefazodone) as well potent inducers of CYP3A (e.g., rifampin, dexamethasone, phenytoin, carbamazepine and phenobarbital) must be avoided and properly reported in the Case Report Format.

2. Side effect associated with Adenosine administration: many individuals experience facial flushing, a temporary rash on the chest, lightheadedness, diaphoresis, or nausea after administration of adenosine due to its vasodilatory effects. Metallic taste is a hallmark side-effect of adenosine administration. These symptoms are transitory, usually lasting less than one minute. It is classically associated with a sense of "impending doom", more prosaically described as apprehension. This lasts a few seconds after administration of a bolus dose, during transient asystole induced by intravenous administration. In some cases, adenosine can make patients' limbs feel numb for about 2–5 minutes after administration intravenously depending on the dosage (usually above 12 mg).

3. Potential complications associated in general with the use of coronary stenting devices or PTCA:

- Acute myocardial infarction
- Allergic reaction to contrast medium/stent material/ medications
- Arrhythmias (including ventricular fibrillation and ventricular tachycardia)
- Arteriovenous fistula
- Bleeding complications
- Cardiac tamponade

- Cerebrovascular accident/stroke
- Death
- Dissection of coronary artery
- Drug reactions
- Embolization (air, stent, tissue or thrombotic)
- Emergency coronary artery bypass graft surgery (CABG)
- Endocarditis
- Failure to deliver the stent
- Stent deformation, collapse or fracture
- Hematoma
- Hemorrhage requiring transfusion
- Injury of the coronary artery
- Myocardial ischemia/infarction
- Pain and tenderness at the insertion site
- Perforation
- Peripheral Ischemia
- Peripheral nerve injury
- Pseudoaneurysm (coronary/ femoral/radial)
- Pyrogenic reaction
- Restenosis of the dilated artery or stented segment
- Sepsis/infection
- Short-term hemodynamic deterioration (hypotension/ hypertension)
- Stent thrombosis or occlusion
- Total occlusion of coronary artery
- Unstable angina
- Vascular thrombosis
- Vessel dissection/perforation/spasm

ACCESS TO SOURCE DATA/DOCUMENTS

The Investigator will permit study-related monitoring, audits, IEC review and regulatory inspections, providing direct access to primary patient data (i.e., source data) which supports the data in the electronic CRFs for the study, i.e., general practice charts, hospital notes, appointment books, original laboratory records etc. Because this enters into the realm of patient confidentiality, this is included in the Informed Consent Form to be signed by the patient.

MONITORING PROCESS

Monitoring of data and access to source documents will be granted upon request to monitors designated by participating hospitals, the study promoter, and principal study investigators.
The monitoring process will be carried out by UCICEC Hospital Clinico San Carlos (Contact: Natalia Pérez Macias – fibucicec.hcsc@salud.madrid.org - +34913303000 ext.7676).

ETHICAL AND LEGAL CONSIDERATIONS

The respect for the rights of the patients will be guaranteed in each phase of the study in accordance with the Declaration of Helsinki and its current revision. The trial will be conducted in accordance with ICH-GCP Guidelines, according to the design of the protocol and with current legal regulation in Spain.

Promotor

The promotor of this study is the Fundación Interhospitalaria de Investigación Cardiovascular (FIC, Paseo San Francisco de Sales 3, 1ºD; 28003 Madrid, Spain).

Ethical Considerations

Before initiating the study, the Investigator shall have written and dated approval /favorable opinion from the relevant IRB / IEC for the study protocol (and any amendments), written informed consent form, consent form updates, patient recruitment procedures (e.g., advertisements), and any other written information to be provided to patients. Approval will be indicated in writing with reference to the final protocol number and date. During the study all documents that are subject to review should be provided to the IRB / IEC by the Investigator. The study promotor will assume the responsibility to obtain all the approval required from IEC.

Independent Ethics Committee (IEC)

This is an independent body (a review board or a committee, institutional, regional, national or international) constituted of medical / scientific professional and non-medical / non scientific members whose responsibility it is to ensure the protection of the rights, safety and well being of human subjects involved in the study, and to provide public assurance of that protection, by reviewing and providing a favorable opinion on the study protocol, suitability of the Investigator, facilities and the methods and material to be used in obtaining and documenting informed consent from study patients.

The legal status, composition, function, operations and regulatory requirements pertaining to the Independent Ethics Committee may differ among countries, but should allow the Ethics Committee to act in agreement with GCP. The investigator agrees to comply with the rules set forth in the applicable clinical trial regulations and Spanish Royal Decree 223/2004 on Clinical Trials. The investigator must submit and, when necessary, obtain approval for all subsequent protocol amendments. The sponsor and the investigators should sign all the amendments.

Informed consent

Informed consent form must be submitted to the Ethics Committee. Before patient signature, the investigator will explain the study and solve any question to the patient. Patient signature is mandatory before randomization and before any study intervention is performed. No subject data will be entered into the study database prior to obtaining written informed consent. In the event that the patient is unable to provide written informed consent, verbal consent from the patient or written assent from a legally acceptable representative will be accepted to facilitate enrolment. The legal representative may provide written consent on behalf of the patient only after having been fully informed about the study. Where a patient is providing verbal consent, an impartial witness must be present during the entire informed consent discussion. Once consent has been given, the witness must sign and personally date the

consent form, to confirm that the information contained within the informed consent and any further information provided by the investigator, was explained to and apparently understood by the patient and that consent was freely given. Where a patient has initially verbally

consented or a patient's legally acceptable representative has assented on behalf of the patient, written consent should be sought from the patient as soon as, in the investigator's opinion, the patient is capable of understanding the process and capable of signing the consent form.

The participation of the patients will be voluntary and no economical compensation will be given to the patients for being part of the study.

Financing and Insurance

The costs necessary to perform the study will be agreed upon with each Investigator and will be documented in a separate financial agreement which will be signed by the Investigator and the promotor, prior to the study commencing.

All participants of this clinical study will be insured against study related injury according to applicable provisions of law with a contracted insurance. The terms of this insurance contract will be revised and approved by the hospital ethical review board. The insurance contract will be signed in accordance with the current regulation in Spain.

Conduct of Study

This clinical study will be conducted in accordance with the Declaration of Helsinki (2013: Seventh revision, 64th Meeting, Fortaleza).

Personal Data and Data Protection

All data obtained in the context of the clinical trial are subject to data protection. The patient's name in addition to other data related to persons (excluding date of birth / age and sex) are not to be disclosed by the Investigator or the investigating physicians. The latter shall take care that the case report forms or other documents (e.g., copies of reports on special findings) transmitted to the review committees or the CRO contain no names, but only either initials or date of birth and / or a random number. The storage of data for electronic statistical assessment shall be performed only under the patient's random / study number. Only the Investigator and the investigating physicians can perform assignment of the identifier to the personal data.

If it becomes necessary in the course of the study to identify a patient's name for medical reasons, all the individuals involved are subject to an obligation to maintain secrecy.

If personal data are stored and processed, the requirements of data protection legislation are to be observed according to the Spanish law ("Ley Orgánica de Protección de Datos de carácter personal 15/1999").

Data Handling and Record Keeping

Completion of Case Report Forms

Case report forms will be maintained in electronic form on an internet based data entry system. The investigator must ensure the accuracy, completeness and timeliness of data

reported in the CRF and all required reports. Data reported on the CRF that are derived from source documents should be consistent with the source documents or the discrepancies should be explained.

Within one week after completion of each patient, the Investigator should agree to have electronically signed CRFs available for full inspection by the clinical monitor.

Archiving

On termination of the trial, the essential documents must be retained until at least 2 years after the last reporting of data in an official manuscript. "Essential documents" are defined as documents that individually and collectively permit evaluation of the conduct of a trial and the quality of the data produced. These documents should be retained for a longer period, however, if required by the applicable regulatory requirements or by an agreement with the sponsor".

Confidentiality

The aim and contents of the study, in addition to its results are to be treated as confidential by all persons involved in the clinical trial.

Responsibilities

The responsibilities of the Investigator, Monitor and Sponsor of the clinical trial as regards handling of data, storage of data, planning, assessment and quality assurance are regulated by the recommendations on "Good Clinical Practice" of the "International Conference on Harmonisation" (ICH) and apply also to this clinical trial.

FINAL REPORT AND PUBLICATION POLICY

It is intended that the results of the study shall be submitted to publication in a peer reviewed journal. At the conclusion of the study, a multicenter abstract reporting the primary results will be prepared by the Principal Investigator, co-principal Investigator and in collaboration with Primary Investigators from high enrolling sites. A multicenter publication will similarly be prepared for publication in a reputable scientific journal. The publication of the principal results from any single center experience within the study is not allowed until both the preparation and publication of the multicenter results. Following analysis and presentation of the primary endpoint results, active participation of all committee members and Investigators will be enthusiastically solicited for data analysis and abstract and manuscript preparation. Submission of all abstracts and publications regarding the primary endpoint and secondary endpoints from the study requires approval by the Study Principal Investigator. According to a good practice in research, negative results must be reported as well as positive findings.

In accordance with generally recognized principles of scientific collaboration, co-authorship with any personnel will be discussed and mutually agreed upon before submission of a manuscript to a publisher.

Appendix

Apendix1 lists all the clinical, angiographic and PCI procedural variables that will be recorded:

Baseline: sex, age, date of index procedure, cardiovascular risk factors (hypertension, dyslipidemia, diabetes, smoke, family history of CAD), chronic kidney disease, previous history of Acute Coronary Syndrome or PCI, number of vessels with stenosis, percentage of stenosis (QCA), Ejection Fraction (EF%),
Laboratory: CK, CK-MB, troponin, hemoglobin, hematocrit, WBC, RBC, thrombocytes, serum creatinine (GFR should be calculated according to Cockroft-Gould),

Apendix 2 lists all the physiology data related to intracoronary assessment at different stages of the study:

Target vessel, basal Pd, basal Pa, basal mean transit time (sec), hyperemic mean transit time (Sec), Pd during hyperemia, Pa during hyperemia, Fractional Flow Reserve (FFR), Coronary Flow Reserve (CFR), Index of Microcirculatory Resistance (IMR).

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Spanish summary

Efecto protector de la microcirculación coronaria de Clopidogrel o Ticagrelor en pacientes con diabetes (PREDICT)

Ensayo clínico multicéntrico aleatorizado usando fisiología intracoronaria multimodal

Versión 1.3

31 May 2017

Centro coordinador

Hospital Clínico San Carlos. Madrid

Promotor

Fundación Interhospitalaria de Investigación Cardiovascular. Madrid

SINOPSIS

Título	Efecto protector de la microcirculación coronaria de Ticagrelor o Clopidogrel en pacientes diabéticos
Introducción	1. La placa coronaria de alto riesgo de embolización distal durante la Intervencionismo coronario percutáneo (ICP) (como aquella con un fibroateroma de cubierta delgada) es más prevalente en pacientes con DM. Esta población tiene, por tanto, alto riesgo de desarrollar un daño miocárdico y microcirculatorio como consecuencia de la ICP. 2. El Ticagrelor inhibe la absorción cellular de adenosina, aumentando los niveles de circulación de adenosina a través de la inhibición de su lavado fisiológico. La adenosina puede proteger al miocardio tanto del daño isquémico como del de la reperfusion a través de sus potentes efectos vasodilatadores y, posiblemente, por sus propiedades antiplaquetarias y antiinflamatorias. 3. La investigación previa de nuestro grupo identificó un efecto aún m´s profundo de la adenosine en la resistencia microcirculatoria asociada con la obesidad y la diabetes y se espera un mayor efecto protector sobre el miocardio del Ticagrelor durante la ICP en este subgrupo de pacientes de alto riesgo.
Hipótesis	En pacientes con DM o pre-DM con enfermedad isquémica del corazón tratados mediante ICP: 1. El Ticagrelor es superior al Clopidogrel en cuanto a la protección de la microcirculación que proporciona durante la ICP; 2. El Ticagrelor es superior al Clopidogrel en la mejora de los parámetros microcirculatorios también antes de la ICP.
Objetivo	Investigar el efecto protector del Ticagrelor en la microcirculación durante la ICP en pacientes con DM o pre-DM.
Estrategia	La evaluación basal de la microcirculación se realizará en los pacientes elegibles antes de la aleatorización de los mismos y su asignación en uno de los grupos (Ticagrelor o Clopidogrel). Después de al menos 48h de tratamiento, se evaluará la function microcirculatoria antes y después de la ICP.
Diseño del estudio	PREDICT es un studio multicéntrico, de diseño abierto, estudio clínico aleatorizado de dos brazos que compara Ticagrelor y Clopidogrel en términos de protección de la microcirculación en pacientes diabéticos que se someten a una ICP.
Número de sujetos	50
Centros participantes	– Hospital Clínico San Carlos, Madrid. Investigador Principal: Javier Escaned; Co-Investigador Principal: Enrico Cerrato. C/Profesor Martín Lagos, s/n; 28040 Madrid. Teléfono: 913303438. – Hospital Galdakao, Bilbao. Investigador Principal local: José Ramón Rumoroso; Barrio Labeaga, s/n; 48960 Usansolo, Vizcaya. Teléfono: 944007000. – Hospital Universitario Puerta de Hierro. Investigador Principal local: Javier Goicolea Ruigomez; Calle Manuel de Falla, 1, 28222 Majadahonda, Madrid. Tel. 911 91 60 00 – Hospital Universitario de Cabueñes. Investigador Principal local: Iñigo

	Lozano Martinez-Luengas. Calle Los Prados, 395, 33394 Gijón, Asturias. Teléfono: 985 18 50 00 (El reclutamiento de pacientes será competitivo hasta alcanzar 50)
Objetivo principal	1. La variación de la resistencia de la microcirculación asociada a la ICP en pacientes con DM o pre-DM tratados con Ticagrelor o Clopidogrel (delta IMR-Post-ICP). 2. La diferencia en la resistencia de la microcirculación asociada al inicio del tratamiento con Ticagrelor en pacientes con DM o pre-DM (delta IMR-Pre-ICP).
Objetivos secundarios	1. Necrosis miocárdica asociada al daño por ICP, evaluada por medio de marcadores cardiacos en pacientes con DM o pre-DM tratados con Ticagrelor o Clopidogrel. 2. Valor absoluto del valor de IMR después de la ICP en pacientes con DM o pre-DM tratados con Ticagrelor o Clopidogrel. 3. Incidencia (%) de lesion severa microcirculatoria (IMR > 29) después de la ICP en pacientes con DM o pre-DM tratados con Ticagrelor o Clopidogrel.
Población de estudio y criterios de inclusión y exclusión	La población de estudio consiste en pacientes con cardiopatía isquémica estable o enfermedad coronaria estable subsidaria de revascularización guiada por FFR (reserva de flujo coronario) y DM o pre-DM referidos a angiografía coronaria en alguno de los centros participantes en el estudio, que presenten estenosis coronarias técnicamente manejables mediante ICP y que puedan ser investigados con guía de presión.. Aquellos pacientes que ya estén en tratamiento con Clopidogrel serán también admitidos en el estudio. Además, esto nos permitirá comparer a los pacientes en tratamiento previo con Clopidogrel con aquellos que solo tomaban aspirina en terminus de delta IMR pre-ICP. **Criterios de inclusión:** + Sujetos con Diabetes Mellitus tipo II o pre-Diabetes Mellitus tipo II. + Sujetos mayores de 18 años. + Consentimiento informado firmado. + Pacientes con cardiopatía isquémica estable o enfermedad coronaria estable, subsidaria de revascularización guiada por FFR (reserva de flujo coronario) aptos para ICP. **Criterios de exclusión:** + Infarto de miocardio previo en el territorio del vaso objetivo. + Akinesia o diskinesia en los segmentos miocárdicos subyacente + El vaso objetivo es un injerto de una vena safena o un injerto quirúrgico se ha anastomosado al vaso objetivo. + Flujo TIMI < 1 antes de cruzar la guía de presión. + El sujeto no es apto para ser tratado con DES. + Desordenes de sangrado o tratamiento anticoagulante crónico. + Estenosis de Tronco Comun mayor del 50% + Cirugía coronaria más beneficiosa para el paciente que la ICP. + Intolerancia o contraindicaciones al tratamiento antiplaquetario. + Contraindicaciones a la administración de adenosina. + Número de plaquetas < 75000 o > 700000/mm3. + Embarazo o lactancia. + Historia de hemorragia intracraneal.

Tratamiento	Grupo experimental Ticagrelor *Dosis de carga*: 180mg *Dosis de mantenimiento*: 90mg bid	Grupo de control Clopidogrel *Dosis de carga*: 600mg *Dosis de mantenimiento:* 75mg die
Promotor	Fundación Interhospitalaria de Investigación Cardiovascular, Madrid	
Investigador Principal	Javier Escaned	
Co-investigador principal	Enrico Cerrato	
Miembros del comité ciéntifico	Javier Goicolea, Iñigo Lozano, José Ramón Rumoroso, Mauro Echavarría-Pinto, Antonio Fernández-Ortiz, Carlos Macaya	
Laboratorio de análisis del estudio	Hospital Clínico San Carlos, Unidad de Cardiología. C/Profesor Martín Lagos, s/n; 28040 Madrid – Tlf.: 913303438 Investigadores colaboradores/Laboratorio de análisis estadístico: Christopher Broyd, Mauro Echavarría-Pinto, Alicia Quirós	

RESUMEN

Los pacientes diabéticos tienen peor pronóstico que los no diabéticos, especialmente en el marco de las ICP. Una función microcirculatoria anormal junto con un mayor riego de embolización distal de partículas derivadas de la lesión revascularizada por ICP constituyen la causa principal de daño microcirculatorial peri-procedimiento.
Los nuevos agentes antiplaquetarios, como el Ticagrelor, pueden jugar un papel en la protección de la microcirculación. El Ticagrelor inhibe la absorción celular de adenosina, aumnetando los niveles de adenosina en circulación a través de la inhibición de su limpiado fisiológico.
La adenosina puede proteger el miocardio tanto de daño isquémico como de reperfusión, a través de su potente efecto vasodilatador y, posiblemente, por sus propiedades anti-inflamatorias y antiplaquetarias.
Además, un trabajo de investigación reciente de nuestro grupo ha identificado un efecto más profundo de la adenonsina en la resistencia microcirculatoria asociada a la obesidad y la diabetes y es razonable esperar un mayor efecto protector por parte del Ticagrelor durante la ICP en este subgrupo de pacientes de alto riesgo.
En el Hospital Clínico San Carlos, planeamos llevar a cabo un ensayo clínico randomizado, prospectivo y original con el objetivo de investigar el efecto protector del Ticagrelor en la microcirculación en el marco de la ICP en pacientes con diabetes mellitus de tipo II o en un estatus pre-diabético.

HIPÓTESIS

En pacientes con DM o pre-DM con enferemedad isquémica del corazón tratados mediante ICP:

1. El Ticagrelor es superior al Clopidogrel en cuanto a la protección de la microcirculación que proporciona durante la ICP;
2. El Ticagrelor es superior al Clopidogrel en la mejora de los parámetros microcirculatorios también antes de la ICP.

OBJETIVOS

Este estudio pretende investigar el efecto protector del Ticagrelor en la microcirculación durante la ICP en pacientes con DM o pre-DM.

OBJETIVO PRIMARIO

1. La diferencia en la resistencia de la microcirculación asociada a la ICP en pacientes con DM o pre-DM tratados con Ticagrelor o Clopidogrel (delta IMR-post-ICP).

2. La diferencia en la resistencia de la microcirculación asociada al inicio del tratamiento con Ticagrelor en pacientes con DM o pre-DM (delta IMR-pre-ICP).

OBJETIVOS SECUNDARIOS

1. Necrosis miocárdica asociada al daño por ICP, evaluada por medio de marcadores cardiacos en pacientes con DM o pre-DM tratados con Ticagrelor o Clopidogrel.

2. Valor absoluto del valor de IMR después de la ICP en pacientes con DM o pre-DM tratados con Ticagrelor o Clopidogrel.

3. Incidencia (%) de lesión severa microcirculatoria (IMR > 29) después de la ICP en pacientes con DM o pre-DM tratados con Ticagrelor o Clopidogrel.

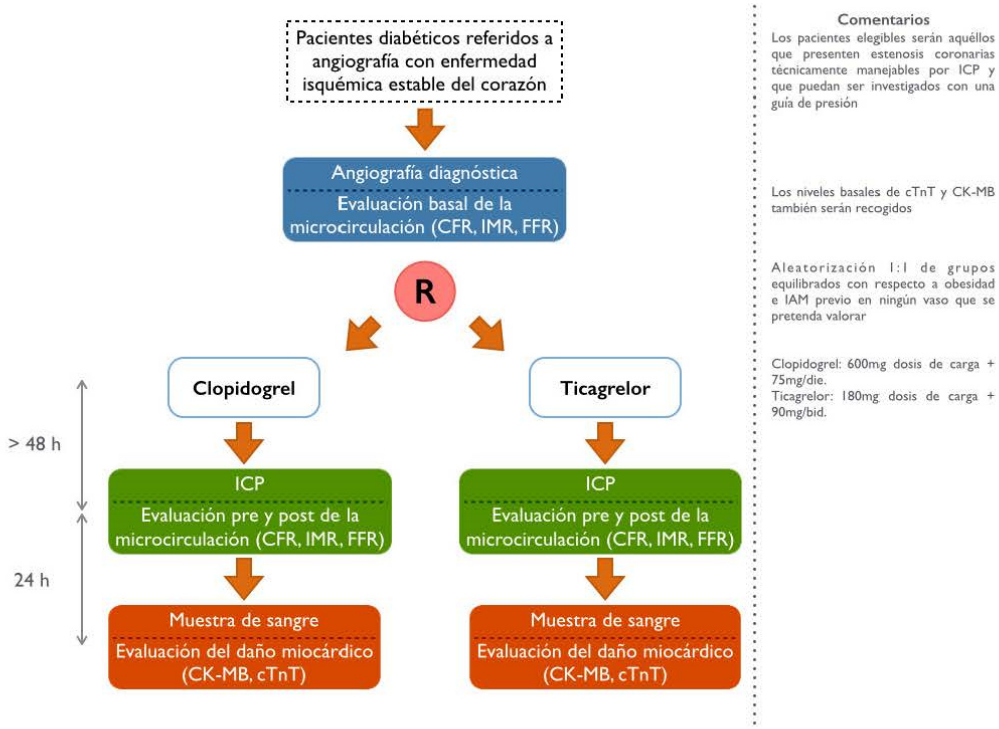
SUBESTUDIO

Dos subgrupos de interés especificados previamente serán los sujetos con obesidad y los pacientes con infarto de miocardio previo en un territorio distinto (diferente al del vaso coronario objetivo). Para estos subgrupos, se implementará una lista de aleatorización dedicada.

DISEÑO DEL ESTUDIO

El estudio será un ensayo clínico aleatorizado que compara dos estrategias terapéuticas. Planeamos llevar a cabo un estudio controlado, aleatorizado, prospectivo y original, que se realizará en el Hospital Clínico San Carlos (Madrid).

Diagrama de flujo y protocolo del estudio



Consentimiento informado

El consentimiento informado se obtendrá después de la angiografía coronaria de diagnóstico. El consentimiento informado será obtenido por un miembro del equipo médico experimentado en un ambiente no coercitivo y en línea con las guías de buena práctica clínica.

Aleatorización

Los pacientes serán asignados aleatoriamente a recibir Clopidogrel o Ticagrelor antes de la ICP. Además, estos grupos serán equilibrados de acuerdo a la prevalencia de obesidad y a la historia previa de infarto, mediante la implementación de listas de aleatorización dedicadas. De esta forma se obtendrán grupos homogéneos. El brazo de estudio se determinará con un sistema de aleatorización digital integrado en el eCRF.

DURACIÓN DEL ESTUDIO

El periodo de reclutamiento de pacientes tiene una duración esperada de 12 meses. Además, se realizará un análisis preliminar después de 6 meses con el objetivo de proporcionar material para una presentación inicial del estudio.

RECOGIDA DE DATOS

El diseño y la gestión de un cuaderno de recogida de datos electrónico (eCRF) dedicado, que será alojado en la plataforma colaborativa CardioGroup.org, formará parte de las tareas de uno de los investigadores (E.C.). Todos los datos serán almacenados de forma segura y confidencial.

2.3.2 Publication No. 5, original article

"PRotective Effect on the coronary microcirculation of patients with DIabetes by Clopidogrel or Ticagrelor (PREDICT): study rationale and design. A randomized multicenter clinical trial using intracoronary multimodal physiology"

Cerrato E, Quirós A, Echavarría-Pinto M, Mejia-Renteria H, Aldazabal A, Ryan N, Gonzalo N, Jimenez-Quevedo P, Nombela-Franco L, Salinas P, Núñez-Gil IJ, Rumoroso JR, Fernández-Ortiz A, Macaya C, Escaned J.

Cardiovasc Diabetol. 2017 May 19;16(1):68. doi: 10.1186/s12933-017-0543-5. PMID: 28526024; PMCID: PMC5438565.

Summary: In T2DM patients a predisposed coronary microcirculation along with a higher risk of distal particulate embolization during PCI increases the risk of peri-procedural microcirculatory damage. which has been associated with endothelial dysfunction, pro-thrombotic state, chronic microvascular dysfunction, increased atheroma burden, vessel wall inflammation, and development of vulnerable plaques prone to distal embolization[6]. However, new antiplatelet agents, in particular Ticagrelor, may protect the microcirculation through its adenosine-mediated vasodilatory effects[7–10]. The present article reported the rationale, design and protocol of the The PRotective Effect on the coronary microcirculation of patients with DIabetes by Clopidogrel or Ticagrelor (PREDICT), a prospective, multicenter, randomized, open-label study designed to investigate the protective effect of Ticagrelor over Clopidogrel on the coronary microcirculation during PCI in patients with T2DM or pre-T2DM. The primary endpoint aims to document (i) a decrease in coronary microcirculatory resistance caused by treatment onset (Ticagrelor > Clopidogrel; mechanistic effect) and (ii) a lower increase in microcirculatory resistance caused by PCI (Ticagrelor < Clopidogrel; protective effect)**.**

STUDY PROTOCOL Open Access

PRotective Effect on the coronary microcirculation of patients with Dlabetes by Clopidogrel or Ticagrelor (PREDICT): study rationale and design. A randomized multicenter clinical trial using intracoronary multimodal physiology

Enrico Cerrato[1,2*], Alicia Quirós[1], Mauro Echavarría-Pinto[1], Hernan Mejia-Renteria[1], Andres Aldazabal[1], Nicola Ryan[1], Nieves Gonzalo[1], Pilar Jimenez-Quevedo[1], Luis Nombela-Franco[1], Pablo Salinas[1], Iván J. Núñez-Gil[1], José Ramón Rumoroso[3], Antonio Fernández-Ortiz[1], Carlos Macaya[1] and Javier Escaned[1]

Abstract

Background: In diabetic patients a predisposed coronary microcirculation along with a higher risk of distal particulate embolization during primary percutaneous intervention (PCI) increases the risk of peri-procedural microcirculatory damage. However, new antiplatelet agents, in particular Ticagrelor, may protect the microcirculation through its adenosine-mediated vasodilatory effects.

Methods: PREDICT is an original, prospective, randomized, multicenter controlled study designed to investigate the protective effect of Ticagrelor on the microcirculation during PCI in patient with diabetes mellitus type 2 or pre-diabetic status. The primary endpoints of this study aim to test (i) the decrease in microcirculatory resistance with antiplatelet therapy (Ticagrelor > Clopidogrel; mechanistic effect) and (ii) the relative microcirculatory protection of Ticagrelor compared to Clopidogrel during PCI (Ticagrelor < Clopidogrel; protective effect).

Conclusions: PREDICT will be the first multicentre clinical trial to test the adenosine-mediated vasodilatory effect of Ticagrelor on the microcirculation during PCI in diabetic patients. The results will provide important insights into the prospective beneficial effect of this drug in preventing microvascular impairment related to PCI (http://www.clinicaltrials.gov No. NCT02698618).

Keywords: Diabetes, IMR, CFR, FFR, Microcirculation, Ticagrelor

Background

Type 2 diabetes mellitus (T2DM) is associated with a significant increase in the risk of coronary artery disease. As the prevalence of diabetes is estimated to double in the next 10 years, the burden of cardiovascular disease associated with this condition will dramatically increase. Although, over the last two decades, cardiovascular mortality has declined considerably in the general population, a similar trend has not been observed amongst diabetic patients [1]. This might be partly explained by the fact that diabetic patients have poorer outcomes than their non-diabetic counterparts [2, 3], both acutely and at long term follow up after coronary revascularization [4]. One of the mechanisms that may be related to this inferior

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outcome is the higher prevalence of periprocedural myocardial infarction (PMI) after percutaneous coronary intervention (PCI) observed in diabetic patients, which has been associated with endothelial dysfunction, prothrombotic state, chronic microvascular dysfunction, increased atheroma burden, vessel wall inflammation, and development of vulnerable plaques prone to distal embolization [5].

New antiplatelet agents, in particular Ticagrelor, might play a protective role in this setting. Ticagrelor, is different to Clopidogrel and other $P2Y_{12}$ inhibitors, as it reduces the physiological clearance of adenosine by inhibiting its cellular uptake, thus increasing the plasma concentration of adenosine. As the primary aim of adenosine is achieving tonic and cellular protection during stress conditions [6], adenosine in turn may protect the myocardium from both ischemic and reperfusion injuries via its potent vasodilator effect and possibly by anti-inflammatory and antiplatelet properties [7].

Additionally, previous research [8] has identified a more pronounced effect of adenosine on microcirculatory resistance in patients with obesity and diabetes. Therefore, a potentially higher protective effect of Ticagrelor during PCI might be expected in this subgroup.

The PREDICT trial was therefore designed to investigate the potential protective effect of Ticagrelor on the coronary microcirculation during PCI in stable T2DM patients.

Rationale

1. Coronary plaques at high risk for distal embolization during PCI [such as those with a thin cap fibroatheroma (TCFA)] are more prevalent in patients with T2DM [5]. Thus, this population is at high risk for developing myocardial injury and microcirculation impairment after PCI.
2. By blocking the ENT1 nucleoside cell membrane transporter, Ticagrelor inhibits cellular uptake of adenosine and thus its physiological clearance, increasing the circulating levels of adenosine. Adenosine may protect the myocardium from both ischemic and reperfusion injuries via its potent vasodilator effect and/or through its anti-inflammatory and antiplatelet properties [7]. Physiologically this may be recognized as a more pronounced decrease in coronary microvascular resistance induced by adenosine after the administration of Ticagrelor [9].
3. Previous research from our group [8] has suggested a more profound vasodilatory effect of adenosine on the microcirculation in patients with obesity and diabetes; these patients may have a greater protective benefit from Ticagrelor during PCI.

Therefore, Ticagrelor may be superior to Clopidogrel in providing microcirculatory protection during PCI procedures in patients with T2DM or pre-T2DM (primary hypothesis). Onset of treatment prior to PCI with Ticagrelor may be followed by a beneficial reduction in coronary microcirculatory parameters, as compared to Clopidogrel (secondary hypothesis).

Methods

Trial design and objectives

The PRotective Effect on the coronary microcirculation of patients with DIabetes by Clopidogrel or Ticagrelor (PREDICT) trial (http://www.clinicaltrials.gov No. NCT02698618) is a prospective, multicenter, randomized, open-label study designed to investigate the protective effect of Ticagrelor over Clopidogrel on the coronary microcirculation during PCI in patients with T2DM or pre-T2DM. The primary endpoint aims to document (i) a decrease in coronary microcirculatory resistance caused by treatment onset (Ticagrelor > Clopidogrel; mechanistic effect) and (ii) a lower increase in microcirculatory resistance caused by PCI (Ticagrelor < Clopidogrel; protective effect). A detailed list of endpoints is reported in Table 1 and defined in the Additional file 1: Appendix. A dedicated eCRF platform will be designed and hosted in the http://www.cardiogroup.org website.

Population recruitment and flow chart

The inclusion and exclusion criteria are listed in Table 2. The target population consists of patients with T2DM or pre-T2DM with stable ischemic heart disease and a single vessel stenosis or multiple vessels with single stenoses technically amenable to PCI and pressure wire study.

The study will be conducted as follows (Fig. 1, flow chart):

Table 1 Study endpoints

Primary
Decrease in microcirculatory resistance caused by treatment onset (Ticagrelor > Clopidogrel)—*mechanistic effect*
Increase in microcirculatory resistance caused PCI (Ticagrelor < Clopidogrel)—*protective effect*
Secondary
Myocardial necrosis associated with PCI damage, assessed by cardiac biomarkers[a]
Absolute resistance value after PCI
Incidence of severe microcirculatory impairment defined as IMR > 29 after PCI
Subgroups analysis
Obese subjects

PCI percutaneous coronary intervention

[a] Third universal definition of myocardial infarction [40]

Table 2 Study inclusion and exclusion criteria

Inclusion criteria
Subject with type 2 diabetes mellitus or pre-type 2 diabetes mellitus status[a]
Subject must be older than 18 years
Written informed consent available
Documented silent ischemia, stable angina or patient who is scheduled for elective revascularization
Subject is eligible for PCI, and PCI target(s) have FFR ≤0.80
Exclusion criteria
Prior myocardial infarction in the territory of the target vessel
Akinesia or dyskinesia in subtended myocardial segments
Severe impairment of left ventricular function (LVEF <35%)
PCI target is a chronic total occlusion
Target lesion has been treated previously (restenotic lesions)
Target vessel is a saphenous vein graft or a surgical graft has been anastomosed to the target vessel
TIMI flow ≤1 prior to guide wire crossing
Subject is not eligible for treatment with drug eluting stent
Bleeding disorders or chronic anticoagulant treatment
Left main stenosis >50%
Coronary surgery deemed more beneficial for the patient than PCI
Ongoing treatment with Ticagrelor
Intolerance or contraindications to anti-platelet drugs
Contraindications for adenosine administration
Platelet count <75,000 or >700,000/mm^3
Pregnant or breast feeding patient
History of intracranial hemorrhage
Severe hepatic impairment

FFR Fractional Flow Reserve, *LVEF* Left Ventricular Ejection Fraction, *PCI* percutaneous coronary intervention, *TIMI* thrombolysis in myocardial infarction

[a] 2014 American Diabetes Association definition [41]

1. Patient identification and enrollment: All consecutive patients with stable ischemic heart disease and T2DM or pre-T2DM referred for coronary angiography will be screened as potentially eligible for the study. Assessment of coronary stenosis severity using Fractional Flow Reserve (FFR) and the status of the microcirculation including measurement of coronary flow reserve (CFR) and Index of Microvascular Resistance (IMR) [10, 11] will be performed with the same pressure guidewire as part of the diagnostic process. Revascularization will be considered whenever a FFR ≤0.80 is found in a stenosis amenable to PCI. Eligible patients requiring PCI will be informed of the characteristics of the study and invited to participate.
2. Randomization: Patients will be randomly assigned (1:1 ratio) to receive either Clopidogrel (600 mg loading dose followed by a daily dose of 75 mg) or Ticagrelor (180 mg loading dose followed by a dose of 90 mg b.i.d). The groups will be balanced according to the presence or absence of obesity [12] (Body Mass Index ≥ 30 kg/m^2) [12] with the implementation of a dedicated randomization list. Patients who are already on oral treatment with Clopidogrel 75 mg/day are allowed to enter the protocol. According to randomization arm these patients will be assigned, after baseline assessment of microcirculation, to continue Clopidogrel 75 mg/day or be switched to Ticagrelor (180 mg loading dose followed by a dose of 90 mg b.i.d).
3. PCI procedure: PCI procedure will be deferred for at least 48 h after the first administration of the study drug treatment in order to allow approximately 5 mean-half life times of their active metabolites, similar to a previously published study [9].
   - 3.1. Pre-PCI: Multimodal physiological evaluation (FFR, CFR, IMR) will be repeated.
   - 3.2. PCI: For all patients undergoing PCI, unfractioned heparin will be administered at the time of PCI. The PCI procedures will be performed using standard techniques using and second generation Drug Eluting Stents. Balloon pre-dilatation will be mandatory before stent implantation using a semi-compliant balloon with a diameter smaller than 75% of the distal reference vessel size in order to avoid confounding effects related to pre-dilation [13]. Post-dilation will be performed according to clinical practice although it will not be mandatory. All PCI characteristics (materials and techniques) will be recorded.
   - 3.3. Post-PCI: After stent implantation, multimodal intracoronary physiological evaluation will be repeated (FFR, CFR, IMR).
4. In-hospital stay: High-sensitivity cardiac troponin and creatine kinase myoband (CK-MB) will be determined in blood samples taken after the intervention (8 and 24 h in all cases, and every 24 up to 72 h in case of rising myocardial markers).
5. In-hospital follow-up and data acquisition: Major adverse cardiac events as well as any bleeding complications occurring during in-hospital stay will be recorded (see Additional file 1: Appendix). All data required to test the primary and secondary endpoints will be collected before hospital discharge.
6. Length of participation: Patients will terminate their study participation at the time of hospital discharge.

Pharmacological treatment(s)

Any concomitant medication used during the study will be recorded as well as any other required medication

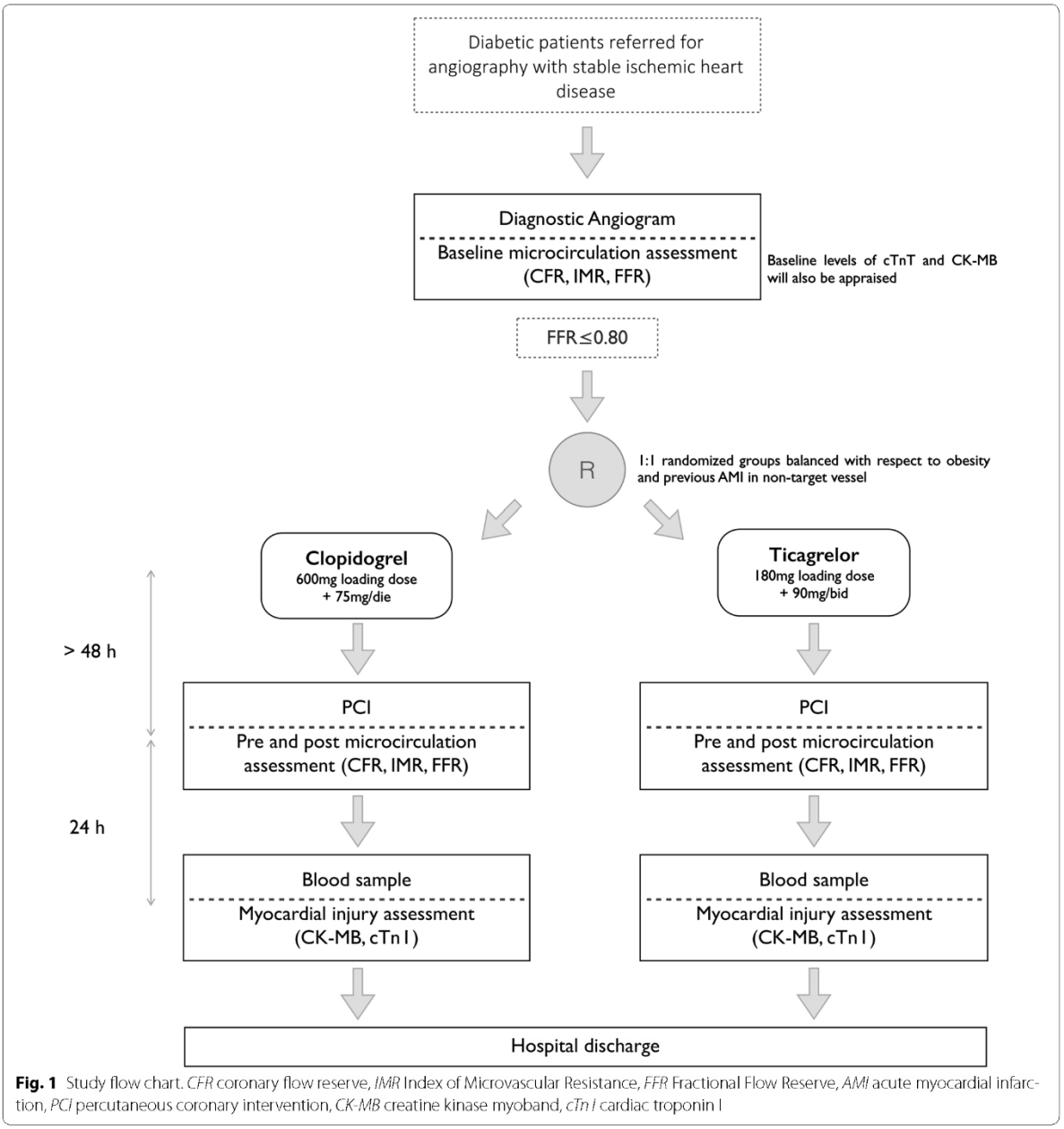

Fig. 1 Study flow chart. *CFR* coronary flow reserve, *IMR* Index of Microvascular Resistance, *FFR* Fractional Flow Reserve, *AMI* acute myocardial infarction, *PCI* percutaneous coronary intervention, *CK-MB* creatine kinase myoband, *cTn I* cardiac troponin I

administered during hospitalization according to current guidelines and clinical practice. Any patients not taking long-term acetylsalicylic acid (ASA) before the procedure will receive a 300 mg oral dose of ASA at the time of inclusion in the study. All patients will continue their chronic treatment after the study termination as prescribed by their cardiologist. Dual antiplatelet therapy regime (DAPT) after discharge will be decided by the responsible physician according to current recommendations, bearing in mind the recommendations on DAPT switching if required [14, 15].

Invasive multimodal physiology assessment

An intracoronary pressure and temperature sensor-tipped guidewire (St. Jude Medical) will be used to measure distal coronary pressure and the index of coronary

flow derived from the coronary thermodilution method as previously described [11]. Three thermodilution curves will be obtained from a hand-held, 3 ml injection of room temperature saline, initially at baseline and then during maximal hyperemia, the latter achieved by an infusion of 140 μg/kg/min of adenosine via a large peripheral vein. Mean transit time (Tmn) at baseline and during maximal hyperemia will be derived from the thermodilution curves. Simultaneous recordings of mean aortic pressure (guiding catheter, Pa) and mean distal coronary pressure (distal pressure sensor, Pd) will be obtained at baseline and during maximal hyperemia. The coronary flow reserve (CFR) will be calculated from the ratio of hyperemic to baseline Tmn. The index of microcirculatory resistance (IMR) will be calculated using the following equation:

$$\mathrm{IMR} = \mathrm{Pa} \times \mathrm{Tmn}\,[(\mathrm{Pd} - \mathrm{Pw})/(\mathrm{Pa} - \mathrm{Pw})],$$

where Pw is the coronary wedge pressure measured during vessel occlusion at the time of PCI. Calculation of IMR using Yong's correction [16] (that does not require the incorporation of Pw) will be performed and reported. The FFR will be calculated from the ratio of distal to proximal pressures at maximal hyperemia.

Sample size and statistical analysis

As no studies are currently available reporting on the impact of Ticagrelor on microvascular function compared to Clopidogrel, we based our sample size calculation on a previous study [10] showing that the intracoronary administration of Nicorandil after PCI resulted in a difference of 10 units in deltaIMR with respect to the control group. Assuming a difference of 10 in deltaIMR, in the experimental vs. control group, and a standard deviation of 10 a total of at least 20 patients per group would be needed to achieve an 80% power at a 2-sided alpha of 0.025, which accounts for the multiple primary endpoint design with a Bonferroni correction. Therefore, we aim to enroll 25 patients per group in order to take into account a 25% of potential missing data or major protocol violation due to clinical reasons (for example: clinical instability of patient between index and PCI procedure leading to urgent revascularization before completion of the protocol).

Any subject who took no trial medication will be eliminated from the full analysis set. Although a low or null proportion of exclusions due to treatment non-compliance is expected, any potential biases arising from this exclusion will be addressed. Imputation techniques will be used in an attempt to compensate for missing data. Regarding missing data, for primary endpoints, listwise deletion will be used meanwhile for the rest of analyses, listwise deletion or multiple imputation will be considered, depending on the type of missing process and on the quantification of the efficiency loss due to case deletion in each case. An investigation will be made concerning the sensitivity of the results of analysis to the method of imputation, especially if the number of missing values is substantial.

Being PREDICT a multicenter trial, the influence of the centre on the treatment effect and other endpoints will be addressed, and further adjustment will be done in the subsequent analysis, if necessary. Special attention will also be paid to the role of baseline measurements of the primary variable and diabetes treatment. Moreover, obese patients and those with previous myocardial infarction are subgroups of interest and their influence on the primary variables will be addressed and interpreted. However, subgroup analyses here have a exploratory nature, and therefore, interpreted cautiously.

A diagram of the participant flow showing for each group, the number of participants who were randomly assigned, received intended treatment, and were analyzed for the primary outcome will be provided, as recommended by the CONSORT 2010 statement.

Categorical variables will be reported as frequencies and percentages. Continuous variables will be expressed as mean ± SD or as median (Q_1–Q_3), according to the normality of their distribution, which will be tested with the Shapiro–Wilk test. Bartlett's test will be performed to demonstrate homogeneity of variances between more than two groups. Primary endpoints will be assessed using the Student *t* test, if the samples are normally distributed or their variances are homogeneous; or Mann–Whitney U test, otherwise. P values will be corrected in order to account for the multiple endpoint. For the analysis of secondary variables, comparisons between continuous variables will be performed using the (paired or unpaired) Student *t* test or Mann–Whitney U test. The IMR at baseline, before PCI, and after PCI will be compared with an ANOVA for repeated measures or with the Friedman test, as appropriate. Comparisons between categorical variables will be evaluated using the Fisher exact test or the Pearson Chi square test, as appropriate. Correlations between continuous variables will be assessed using the Pearson or the Spearman rank correlation test. A 2-way ANOVA for repeated measures will be used to detect changes in IMR levels over time in the two study groups. Finally linear and logistic regression models will be carried out in order to identify predictors of periprocedural myonecrosis and delta-IMR. Analysis will be performed both in the full analysis set and a per protocol analysis and any differences between them would be the subject of explicit discussion and interpretation. In case of having multiple stenoses in some patient, additional adjusted analysis will be provided. Statistical analyses will

be performed using the R statistical software [17] and p values <0.05 (2-tailed) will be considered significant. Whenever possible, estimates will be accompanied by confidence intervals.

Participating centers

PREDICT will be coordinated by Hospital Clínico San Carlos (Madrid, Spain). Other three centers in Spain will participate in patient enrollment: Hospital de Galdakao (Bilbao), Hospital Universitario de Cabueñes (Gijón), Hospital Puerta de Hierro, Majadahonda.

Discussion

The main purpose of the PREDICT trial is to test if Ticagrelor provides greater protection to the coronary microcirculation during PCI in diabetic patients compared to Clopidogrel as assessed by microvascular resistance indices. The results will provide important insights into the prospective beneficial effect of this drug in preventing microvascular impairment related to PCI. In the following paragraphs, we briefly discuss the rationale behind our study hypothesis.

Microcirculatory damage during percutaneous coronary interventions

Instrumentation of atheromatous vessels during PCI, such as balloon dilation or stent implantation, may damage the subtended microcirculation and myocardium. The most dramatic presentation of this phenomenon is the so-called no-reflow phenomenon [18], in which coronary flow is interrupted or severely impaired despite the absence of epicardial obstruction, causing acute ECG and hemodynamic disturbances and a variable degree of myocardial damage. However, in most cases peri-procedural myocardial damage has a much more subtle presentation or is even clinically unnoticed. Distal embolization of particles released from the PCI target lesion constitutes the main cause of peri-procedural microcirculatory damage [19]. In stable patients, micro-emboli have an origin in atheromatous plaque, mainly derived from cholesterol rich deposits named atheromatous gruel. Several studies [20] using virtual histology Intra Vascular Ultrasound (VH-IVUS), frequency-domain optical coherence tomography (FD-OCT) and near infrared spectroscopy (NIRS) have linked the occurrence of the no-reflow phenomenon following PCI to cholesterol-rich plaques, mainly thin cap fibroatheromas. The same techniques have documented a higher prevalence of these types of plaques in patients with T2DM [5], who typically constitutes a higher-risk subset of patients for PCI treatment. Patients with diabetes often have comorbidities and a greater burden of coronary artery disease [21]. However, despite correction for these factors, diabetic patients still consistently have poorer outcomes than their non-diabetic counterparts especially in the setting of PCI [2, 3]. The abnormal coronary microcirculation [22] along with the higher risk of peri-procedural microcirculatory damage in T2DM represents one of the harmful and still unmet issues potentially connected with a poor long-term outcome. Additionally, even an optimal glycaemic control (HbA1c < 7%) does not predict a better coronary microcirculatory function in T2DM [23] claiming for a more appropriate strategies for prevention of coronary microvascular dysfunction.

Several authors have proposed pharmacological strategies targeting the microcirculation to prevent peri-procedural damage. As cardiac biomarker release is a vague indicator of microcirculatory damage (it may occur as a result of small side branch occlusion unnoticed in angiography), the use of physiological techniques to measure modifications in microcirculatory resistance (such as the IMR) has been advocated [11] as a surrogate of microcirculatory damage. IMR is reproducible, and mounting evidence supports its value as a meaningful diagnostic tool, particularly immediately after PCI. IMR values > 32 U (median) have been associated with higher infarction size (as assessed by CK-MB) and worse wall motion score at 3 months assessed by echocardiography. Moreover, IMR has been found to be the only significant predictor of recovery of LV function after ST Elevation Miocardial Infarction (STEMI) and previous studies conducted in T2DM patients demonstrated that post-PCI IMR is higher compared to non-T2DM individuals.

$P2Y_{12}$ receptors inhibitors: platelet reactivity and endothelial function

In patient with stable CAD, addition of Clopidogrel therapy results in an increase in endothelial function at the primary endpoint (assessed via reactive hyperaemic index) of 3 months. The improvement in endothelial function was already evident after 1 week of Clopidogrel therapy and seems to be not related to Clopidogrel effects on platelet aggregation [24].

On the other hand, among patients, those with T2DM exhibited increased platelet reactivity compared to patients without diabetes despite combined treatment with Clopidogrel and aspirin even when a loading dose of Clopidogrel rather than small daily doses was used [25]. The mechanisms leading to the high on-treatment platelet reactivity in T2DM patients are not fully elucidated and could potentially involved genetic factors [26].

Thus, after the introduction of new $P2Y_{12}$ agents, the influence of Prasugrel or Ticagrelor on platelet reactivity in T2DM patients was object of studies demonstrating that Ticagrelor treated patients have overall lower platelet reactivity than patients on Prasugrel, independently of T2DM

status or insulin treatment [27]. The effects of Prasugrel versus Clopidogrel on Coronary microvascular function in patients undergoing elective PCI was recently reported by Mangiacapra et al. [28] in the PROtecting MICROcirculation during coronary angioplasty (PROMICRO-2) trial. Compared with baseline, IMR increased post-PCI in the Clopidogrel group ($p = 0.009$), but not in the Prasugrel group ($p = 0.299$). Despite some limitations (small sample size; single time point measurement of IMR post-PCI; lack of intracoronary imaging for assessment of plaque burden) the result of this trial suggest that more intensive antiplatelet regimens might offer additional benefit compared with Clopidogrel also in the setting of elective PCI.

An ongoing randomised, prospective, controlled study [29] are also testing the effect of Clopidogrel, Prasugrel and Ticagrelor on multiple parameters of vascular function, platelet aggregation, oxidative and inflammatory stress before and up to 1 month after coronary artery stenting.

Ticagrelor and adenosine metabolism

Beyond the antagonizing effect on $P2Y_{12}$ receptors and the improvement in microvascular endothelial function that we reported above, Ticagrelor may also protect microcirculation increasing the circulating levels of adenosine, Several studies have consistently shown that Ticagrelor inhibits the cellular uptake of adenosine. Intracellular adenosine is rapidly uptaken and metabolized to inosine by adenosine deaminase or transformed into adenine nucleotides by adenosine kinase [7] and therefore by inhibiting its transport into cells its half-life can be increased. Ticagrelor achieves this by inhibiting the sodium-independent nucleoside transporter 1 (ENT1) [30] leading to significantly conserved adenosine levels in human whole blood in vitro experiments. Finally, a wide spectrum of biological effects and physiological responses are carried out through a pathway mediated by adenosine interaction with at least four different receptor subtypes (A1R, A2AR, A2BR, and A3R) which are coupled to stimulatory or inhibitory G proteins [31].

Wittfeldt et al. [9] first demonstrated an adenosine related mode of action for Ticagrelor in humans. In a double-blind, placebo-controlled, crossover study Coronary Blood Flow Velocity (CBFV) was measured using transthoracic Doppler echocardiography at rest after multiple stepwise adenosine infusions. Ticagrelor increases the adenosine-induced physiological responses as shown by an increased area under the curve (AUC) for CBFV response compared to placebo. This increase correlated with plasma Ticagrelor concentrations and was mediated by adenosine receptors with a reversal of this effect after infusion of theophylline, a non-selective competitive adenosine receptor antagonist.

Protective effects of adenosine on myocardial injury associated with percutaneous interventions or acute coronary syndromes

Adenosine is routinely used in the catheterization laboratory for the treatment of the no-reflow phenomenon during PCI, which constitutes an extreme manifestation of peri-procedural damage. No-reflow develops dramatically in response to vessel instrumentation, with contrast medium stagnation in epicardial arteries, persistent myocardial blush and, frequently, accompanying ECG and hemodynamic changes. This complication is the result of plugging of the coronary microcirculation by downstream embolization of micro-thrombi or atheroma dislodged from the culprit lesion as a result of its manipulation during PCI [32]. Reperfusion injury may also manifest as no-reflow phenomenon. A protective effect of adenosine administration in preventing ischemia/reperfusion injury has been demonstrated in both humans [33] and animal models [34].

The effects of adenosine on no-reflow have been investigated in numerous studies. A recent meta-analysis of seven randomized clinical trials supports the benefit of intracoronary adenosine in terms of post-PCI ST-segment resolution and reduced residual ST-segment elevation [35]. Additionally, the PROMISE trial recently showed a reduction in infarct size in patients undergoing administration of high-dose intracoronary adenosine [36]. These effects may be related to the potent vasodilatory effects and potential anti-inflammatory and antiplatelet properties of adenosine. Finally, the CV-TIME trial [37] recently demonstrated that in patients with STEMI treated by primary PCI, a 180 mg loading dose of Ticagrelor might be more effective in reducing microvascular injury than a 600 mg loading dose of Clopidogrel, as demonstrated by IMR immediately after primary PCI.

Microcirculatory and systemic responses to adenosine

The response after adenosine administration is heterogeneous and associated with relevant differences in clinical and intracoronary physiological characteristics. Based on a study performed with intracoronary multimodal physiology, we recently reported that patients with T2DM or the metabolic syndrome [8] demonstrate enhanced responses to adenosine both at a systemic and coronary microcirculatory level (as shown by a drop in systemic blood pressure and microcirculatory resistance). A possible explanation for this observation may be related to the heterogeneous impairment in adenosine receptor subtypes A1 reported in obese humans compared to non-obese [38].

This finding supports the hypothesis that the myocardial protective effect of Ticagrelor may be higher in patients with T2DM or the metabolic syndrome. This is

of particular importance, as PCI in patients with diabetes has been associated with higher peri-procedural events than in non-diabetic patients.

Conclusions

The role of adenosine in protecting the microcirculation remains controversial [39]. This property of adenosine may be particularly important in the context of high-risk patients such as diabetics. PREDICT will be the first randomized multicenter clinical trial to test the adenosine-mediated vasodilator effect of Ticagrelor on the microcirculation during PCI in diabetic patients. The results will provide important insights into the prospective beneficial effect of this drug in preventing microvascular impairment related to PCI.

Additional file

Additional file 1: Appendix. Definitions and outcomes.

Abbreviations

AMI: acute myocardial infarction; AUC: area under the curve; BMI: Body Mass Index; CBFV: Coronary Blood Flow Velocity; CFR: coronary flow reserve; CK-MB: creatine kinase myoband; C Tn I: cardiac troponin I; DAPT: dual antiplatelet therapy; ECG: 12-leads electrocardiogram; ENT1: sodium-independent nucleoside transporter 1; FD-OCT: frequency-domain optical coherence tomography; FFR: Fractional Flow Reserve; FPG: fasting plasma glucose; GFR: glomerular filtration rate; HbA1c: glycosylated hemoglobin; HDL: high density lipoprotein cholesterol; IFG: impaired fasting glucose; IMR: Index of Microvascular Resistance; IVUS: Intra Vascular Ultrasound; LDL: low density lipoprotein cholesterol; LVEF: Left Ventricular Ejection Fraction (%); MACEs: major cardiovascular events; NIRS: near infrared spectroscopy; OGTT: oral glucose tolerance test; PCI: percutaneous coronary intervention; STEMI: ST Elevation Miocardial Infarction; T2DM: type 2 diabetes mellitus; TCFA: thin-cap fibroatheroma; TIMI: Thrombolisis in Myocardial Infarction Flow; VH-IVUS: virtual histology Intra Vascular Ultrasound; WHO: World Health Organisation.

Authors' contributions

EC and AQ drafted the manuscript. EC, AQ and JE designed the study and wrote the original study protocol. JE and EC are responsible for conducting the trial as primary investigators and gave final approval for submission of this manuscript. ME-P, HM-R, AA, NR, NG, PJ-Q, LN-F, PS, IN-G, JRR,IL, AF-O, CM revised the manuscript for important intellectual content. All authors read and approved the final manuscript.

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Competing interests

The authors declare that they have no competing interests.

Disclosures

All authors report no relevant relationships to the content of this paper.

Ethics approval and consent to participate

The local Institutional Review Board of each participating hospital reviewed and approved this study with final resolution on December the 17th, 2015 (internal code 15/526-R). In addition, written informed consent will be obtained from all participants.

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2.3.3 PREDICT: data collection, statistical analysis and results

2.3.3.1. Study Data Collection

The study received a grant from industry and was approved by the Ethical Committee in Hospital Clinico San Carlos, Madrid. The protocol was therefore implemented in three centers in Spain. The enrollment started in September 2016 in the coordinatedspital center in Madrid. Subsequently, after few months two other centers were implemented (Hospital Galdakao, Bilbao, H. de Cabueñes, Gijón).

A dedicated eCRF platform was properly designed and hosted in the collaborative research website Cardiogroup.org. (http://www.cardiogroup.org/PREDICT: **Figure 1**). An external monitor was in charge to check completion and accuracy of the data.

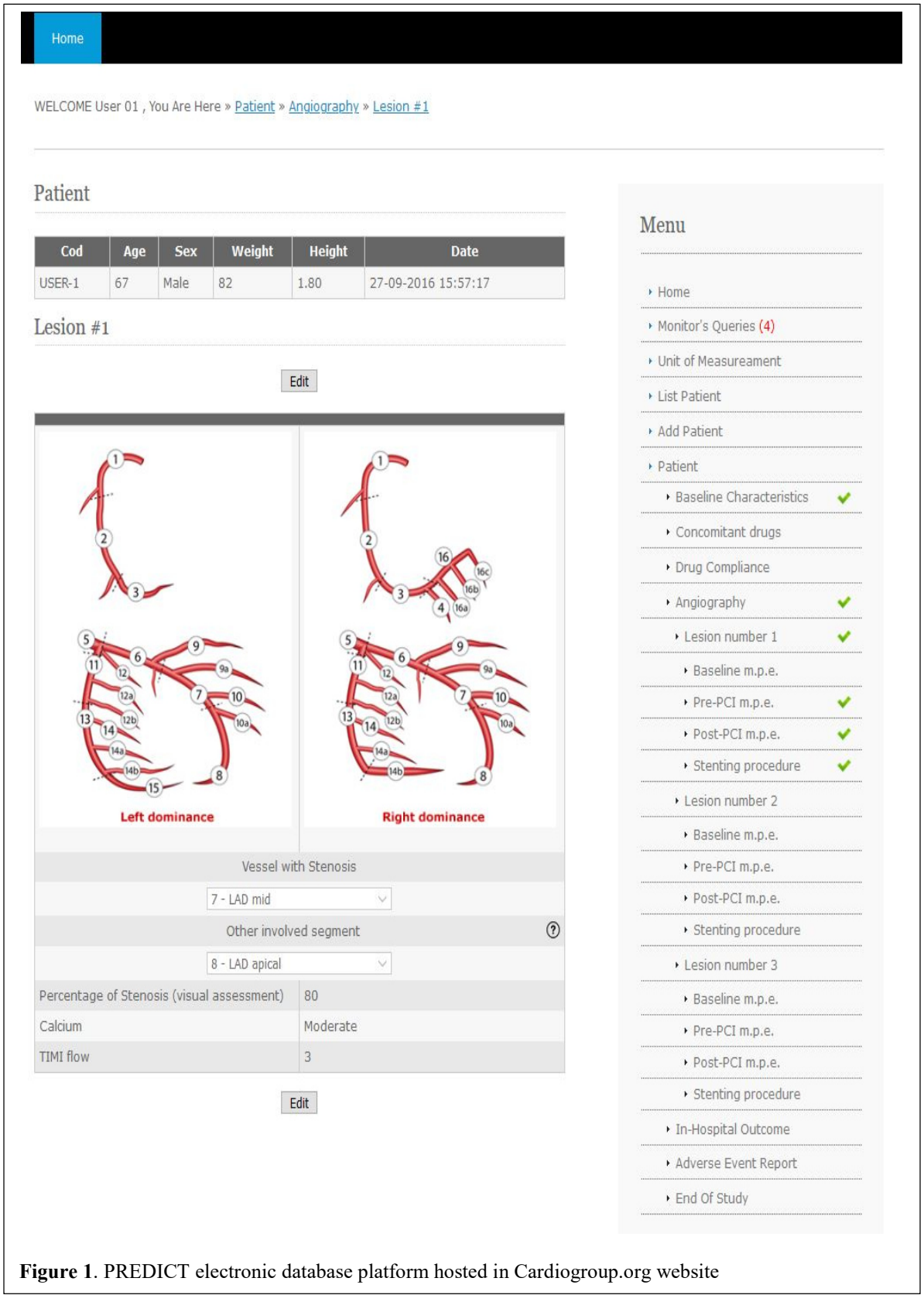

Figure 1. PREDICT electronic database platform hosted in Cardiogroup.org website

2.3.3.3. Statistical analysis

As recommended by the CONSORT 2010 statement[11], **figure 2** depicts the flow diagram of the study's enrollment, showing that 25 subjects were assessed for eligibility, of whom 22 where randomized, half of them to Ticagrelor arm. All subjects received the intended treatment and completed trial medication, hence full analysis set was composed by 11 subjects (12 vessels) in the Clopidogrel arm and 11 subjects (11 vessels) in the Ticagrelor arm. Listwise deletion was used for primary endpoint analysis, in the cases in which it was not measured or a problem with the quality of data was detected in one of more physiological measurement, after a careful review from the central core lab in Hospital Clinico San Carlos, Madrid. Categorical variables are reported as count (percentage). Continuous variables are expressed as mean ± SD or as median (Q_1 – Q_3), according to the normality of their distribution, which will be tested with the Shapiro-Wilk test. All physiological indices are reported using mean ± SD regardless of the nature of their distribution allowing an easier comparison with other publications' results. Bartlett's test was performed to demonstrate homogeneity of variances between more than two groups. Primary endpoint was assessed using the Student t-test. For the analysis of secondary variables, comparisons between continuous variables were performed using the (paired or unpaired) Student t-test or Mann-Whitney U test, according to te normality of their distribution and the homogeneity of their variances between groups. The baseline, pre-PCI, and post-PCI FFR, CFR, and IMR were compared with an ANOVA. Comparisons between categorical variables were evaluated using the Fisher exact test or the Pearson χ^2 test, as appropriate. Correlations between continuous variables were assessed using the Pearson or the Spearman rank correlation test. A two-way ANOVA was used to detect changes in IMR levels over time in the two study groups. Obese patients are a subgroup of interest and its influence on the primary variables was addresses. Statistical analysis

was performed using the R statistical software[12] and p-values < 0.050 (2-tailed) were considered significant.

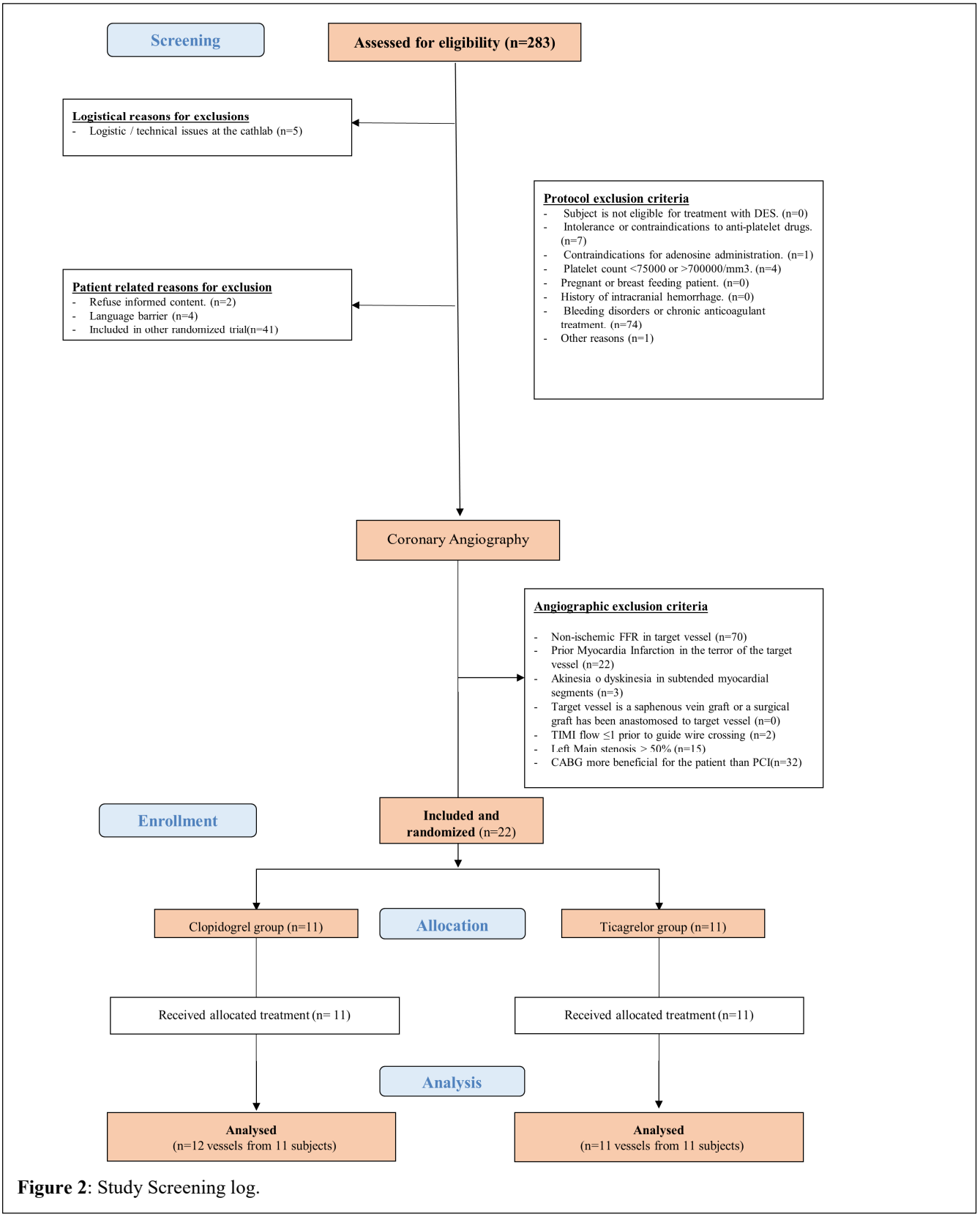

Figure 2: Study Screening log.

2.3.3.3. Results

2.3.3.3.1 Premises

The PREDICT trial study was prematurely halted because of low rate of enrollment by the steering committee. The reasons were many and can be summarized as follows:

a. Refusal: patients entering in the protocol should accept to remain in-hospital for at least 3 days to repeat cardiac catheterization finally performing PCI. Being patients referred for a SIHD (and not for an ACS), the length of in-hospital stay is significantly extended in case of entering in the protocol.
b. Logistics: as stated above, patients must prolong in-hospital stay for at least 3 days to complete the protocol or alternatively had to be readmitted for a scheduled PCI.
c. Coronary anatomy: T2DM with SIHD present most frequently with a MVD with high anatomical complexity. In this case they must be considered as candidates for surgical revascularization with Coronary Artery Bypass Grafting (CABG)[1] and consequently they were excluded from the protocol. Even in case of stenosis deemed suitable for PCI, we had to exclude complex anatomical subset like LMCA stenosis, restenosis, chronic total occlusions etc. in order not to generate bias when assessing the microcirculatory status. This conditions are well known to be more frequent in T2DM patients.[13]
d. Physiological assessment: when performing FFR in intermediate stenosis, a non-ischemic value (FFR > 0.80) can be registered in up to 30% of cases and consequently PCI was unnecessary.
e. Study drug: in order to maximize the enrollment, we also screened diabetic patients previously admitted for ACS and scheduled to perform a physiological assessment on a non-infarct related vessel during a staged post-dicharge procedure. However, in this case almost all patients were already on treatment with Ticagrelor and were therefore excluded from the protocol (only “naïve” patients or patients on Clopidogrel are admitted). This fact occurred because DAPT with use of potent P2Y12 inhibitors (as Ticagrelor) was recommended over Clopidogrel with a class I, level of evidence B in 2014 European Guidelines[14] after the design of our study protocol.

An interim analysis was therefore performed including 22 patients / 23 vessels and the steering committee decided to stop the trial and report study results

2.3.3.3.2 Final study population

A total of 22 patients were randomized to Clopidogrel (11) and Ticagrelor (11) groups. The baseline characteristics of the patients are shown in **Table 1**. Data from a total of 23 vessels was observed, of which 12 corresponded to patients randomized to Clopidogrel group and 11 to patients in the Ticagrelor group. Vessel and treatment characteristics are summarized in **Table 2**. Tables demonstrate that randomization balanced the samples in terms of baseline clinical and vessel characteristics.

	All patients (n = 22)	**Clopidogrel (n = 11)**	**Ticagrelor (n =11)**	**p-value**
Age	69.1 ± 12.1	69.8 ± 12.6	68.3 ± 12.2	0.773
Sex Male	17 (74%)	9 (82%)	8 (73%)	0.999
Body mass index	29.6 ± 3.5	30.1 ± 3.1	29.1 ± 3.9	0.505
Hypertension	19 (90%)	11 (100%)	8 (80%)	0.214
Dyslipidemia	17 (81%)	9 (82%)	8 (80%)	0.999
Smoker				0.102
Active	3 (14%)	0 (0%)	3 (30%)	
Former	10 (48%)	7 (64%)	3 (30%)	
Never	8 (38%)	4 (36%)	4 (40%)	
Severe Chronic kidney disease (eGFR<30)	5 (25%)	3 (27%)	2 (22%)	0.999
COPD	0 (0%)	0 (0%)	0 (0%)	-
Previous myocardial infarction	3 (15%)	1 (9%)	2 (20%)	0.587
Ejection Fraction (%)	60 (60 - 64)	60 (60 - 64.5)	60 (56.3 - 60)	0.582
Hemoglobin (gr/dl)	13.0 ± 1.5	13.3 ± 1.3	12.7 ± 1.7	0.442
Creatinine (mg/dl)	0.96 (0.87 - 1.13)	0.97 (0.89 - 1.15)	0.95 (0.87 - 1.02)	0.595
MRDR	76.7 ± 29.8	73.4 ± 26.1	80.7 ± 34.9	0.612
Glycated Hb (%)	6.8 ± 1.4	6.9 ± 1.4	6.6 ± 0.6	0.567

Table 1 Baseline characteristics of the patients, full sample and by groups. P-values refer to group comparison. eGFR: estimated Glomerular Filtration Rate. Hb: Hemoglobin.

	All vessels (n = 23)	Clopidogrel (n = 12)	Ticagrelor (n = 11)	p-value
Vessel				0.604
- **LCX**	5 (25%)	3 (27%)	2 (22%)	
- **LAD**	14 (70%)	7 (64%)	7 (78%)	
- **RCA**	1 (5%)	1 (9%)	0 (0%)	
% stenosis (visual assessment)	80 (74 – 80)	80 (75 – 80)	80 (60 – 80)	0.369
Calcium				0.243
- **Mild**	12 (60%)	7 (64%)	5 (56%)	
- **Moderate**	6 (30%)	2 (18%)	4 (44%)	
- **Severe**	2 (10%)	2 (18%)	0 (0%)	
Pre-dilatation	17 (81%)	8 (67%)	9 (100%)	0.173
Stent implanted	1 (1 – 1)	1 (1 – 1.25)	1 (1 – 1)	0.465
Stent diameter (mm)	2.75 (2.5 – 3)	3 (2.7 – 3.1)	2.5 (2.5 – 2.75)	0.100
Stent length (mm)	24 (15 – 32)	18 (15 – 35)	24 (19 – 32)	0.803
Post-dilatation				0.121
- **No**	7 (33%)	6 (50%)	1 (11%)	
- **Non-compliant balloon**	10 (48%)	5 (42%)	5 (56%)	
- **Semi-compliant balloon**	4 (19%)	1 (8%)	3 (33%)	
Intracoronary imaging	2 (10%)	1 (8%)	1 (11%)	0.999

Table 2: Vessel and treatment characteristics. Full sample and by groups. P-values refer to group comparison. LCX: Left Circunflex Artery; LAD: Left Anterior Descending; RCA: Right Coronary Artery.

2.3.3.3.3 Intracoronary hemodynamic physiology

FFR, CFR IMR were measured at enrolment, before and after PCI. From first drug administration to pre-PCI measurement the time on treatment was 82.2±35.6 hours without difference among groups (74.8±34.0 in Clopidogrel group vs 89.4±37.3 in Ticagrelor group, p=0.857)

All indices were measured with a coronary pressure/temperature wire (Certus, Abbott, St. Paul, MN) as previously reported in the study protocol. All measurements were extracted from the RadiAnalyzer Xpress, and all traces were analyzed offline by an independent blinded expert locally using RadiView Software (Abbott). A second independent operator checked all analyzed traces evaluating also the quality of traces and discussing with the first operator in cases of discordance until achieving a consensus.

All values are shown in **Table 3** and graphically represented in **figures 3a** (FFR), **3b** (CFR) and **3c** (IMR). While at baseline there were no differences in IMR values between groups, new measurement of IMR before PCI revealed significantly lower values in patients who had been randomized to Ticagrelor than to Clopidogrel treatment (13.71 ± 3.70 vs. 20.77 ± 5.43 respectively, **p=0.004**) while not significant differences in IMR values were observed post PCI between study groups. No significant difference were observed in CRF values between groups at any of the 3 stages of data collection. As expected, FFR values significantly improved after revascularization.

	Clopidogrel (n = 12)	Ticagrelor (n = 11)	p-value
Fractional flow reserve			
Basal	0.69 ± 0.12	0.62 ± 0.07	0.161
Pre-PCI	0.68 ± 0.14	0.65 ± 0.07	0.501
Post-PCI	0.89 ± 0.06	0.83 ± 0.10	0.169
p-value	**<0.001**	**<0.001**	
Coronary flow reserve			
Basal	1.50 ± 0.89	1.86 ± 0.75	0.310
Pre-PCI	1.68 ± 0.89	1.39 ± 0.27	0.350
Post-PCI	2.53 ± 1.59	1.85 ± 0.84	0.249
p-value	0.103	0.246	
Index of microvascular resistance			
Basal	17.39 ± 10.03	15.67 ± 4.63	0.617
Pre-PCI	20.77 ± 5.43	13.71 ± 3.70	**0.004**
Post-PCI	17.50 ± 14.39	15.67 ± 6.39	0.725
p-value	0.717	0.632	

Table 3: Physiology indices, measured along the study, for all the sample and by groups. P-values refer to group comparison.

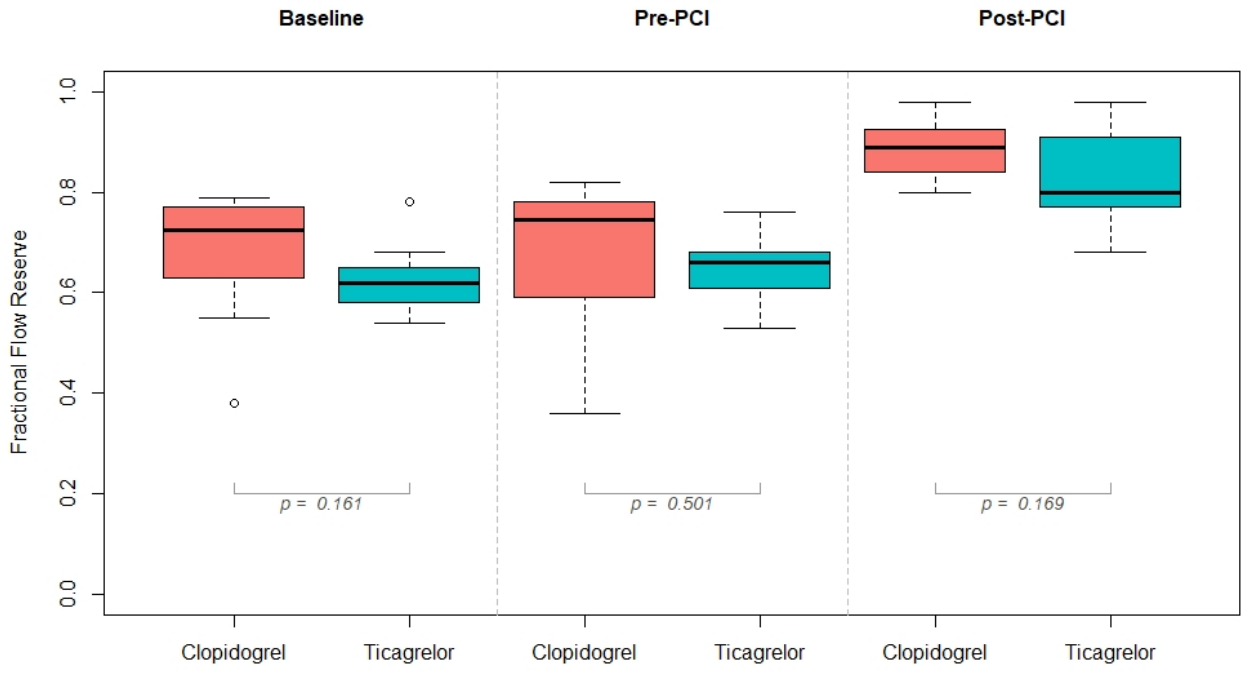

Figure 3a: **Fractional Flow Reserve** in patients randomized to Ticagrelor or Clopidogrel. No significant difference is seen in Coronary Flow Reserve between patients randomized to Ticagrelor and those randomized to Clopidogrel during the index (basal), pre-PCI and post-PCI measurements. Median values are denoted; the cross marks the mean value. Whiskers represent the minimal to maximal values with the median in between.

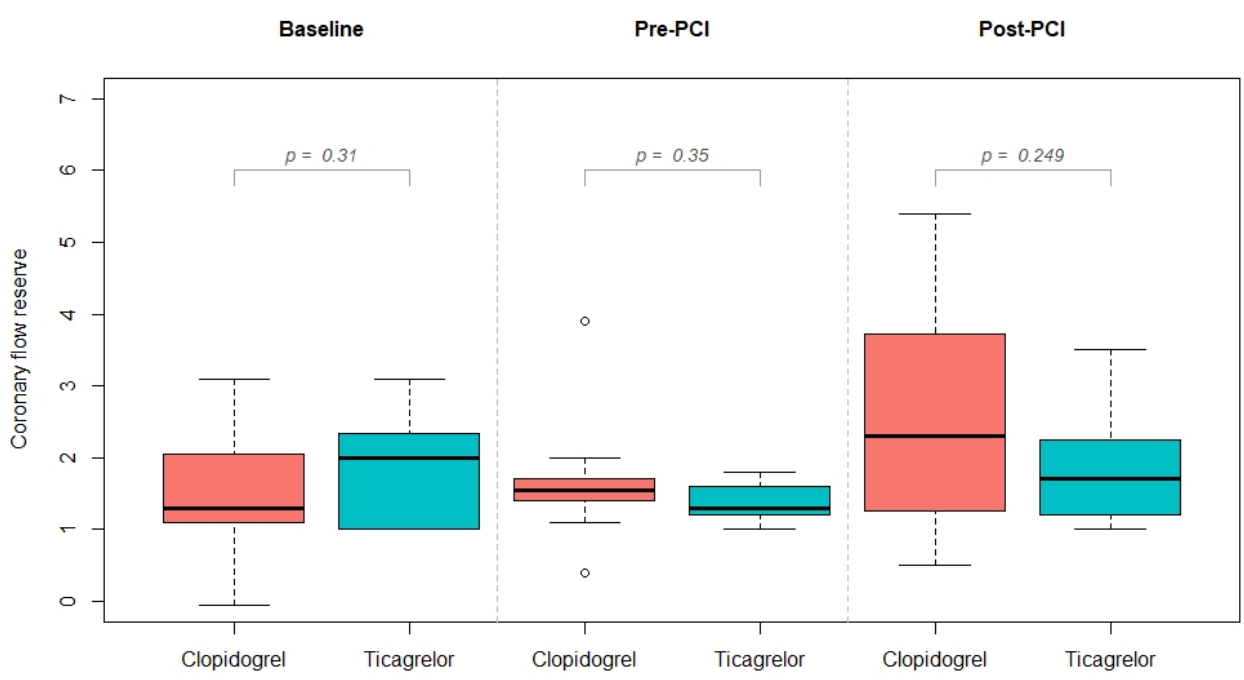

Figure 3b: **Coronary Flow Reserve** in patients randomized to Ticagrelor or Clopidogrel. No significant difference is seen in Coronary Flow Reserve between patients randomized to Ticagrelor and those randomized to Clopidogrel during the index (basal), pre-PCI and post-PCI measurements. Median values are denoted; the cross marks the mean value. Whiskers represent the minimal to maximal values with the median in between.

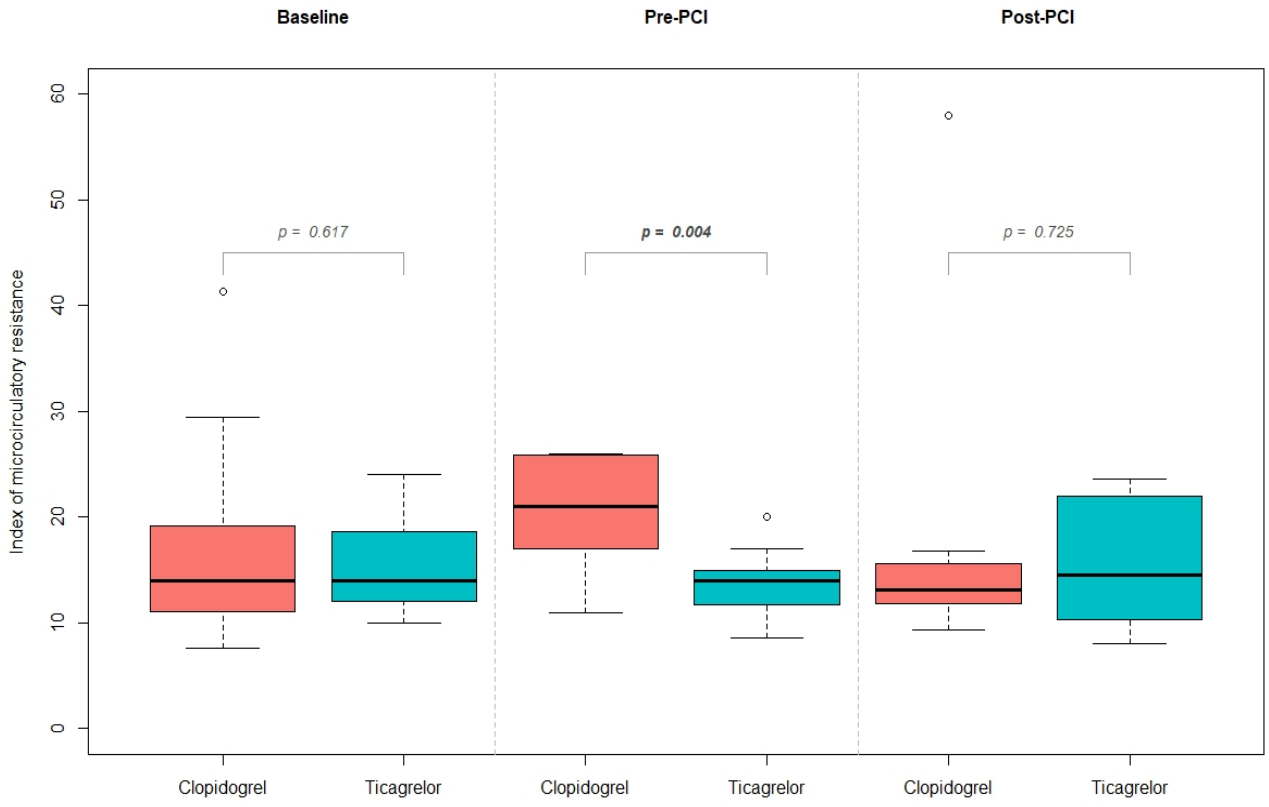

Figure 3c: Index of microcirculatory resistance in patients randomized to Ticagrelor or Clopidogrel. Significant difference is seen in Index of microcirculatory resistance between patients randomized to Ticagrelor and those randomized to Clopidogrel during the pre-PCI measurement while no differences are present at basal and post-PCI. Median values are denoted; the cross marks the mean value. Whiskers represent the minimal to maximal values with the median in between.

2.3.3.3.4. Primary endpoints

A. Decrease in microcirculatory resistance caused by treatment onset.

Define

$$\Delta\mathrm{IMR}_{\mathrm{pre}} = \mathrm{IMR}_{\mathrm{pre}} - \mathrm{IMR}_{\mathrm{basal}}$$

$\Delta\mathrm{IMR}_{\mathrm{pre}}$ was significantly different between groups (Clopidogrel: 4.97 $\pm$ 8.4; Ticagrelor: -2.36 $\pm$ 4.6; $\boldsymbol{p}$**-value = 0.039**). **Figure 4, left panel** shows $\Delta\mathrm{IMR}_{\mathrm{pre}}$ for Clopidogrel and Ticagrelor groups.

A decrease in $\Delta\mathrm{IMR}_{\mathrm{pre}}$ ($\Delta\mathrm{IMR}_{\mathrm{pre}} < 0$) was observed in 3 (33%) vessels in Clopidogrel group, and in 5 (55%) vessels in Ticagrelor group (p-value = 0.637).

B. Increase in microcirculatory resistance caused by PCI.

Define

$$\Delta\mathrm{IMR}_{\mathrm{post}} = \mathrm{IMR}_{\mathrm{post}} - \mathrm{IMR}_{\mathrm{pre}}$$

$\Delta\mathrm{IMR}_{\mathrm{post}}$ was not significant different between groups (Clopidogrel: -2.27 $\pm$ 20.29; Ticagrelor: 1.32 $\pm$ 6.87; p-value = 0.647). **Figure 4, right panel** shows $\Delta\mathrm{IMR}_{\mathrm{post}}$ for Clopidogrel and Ticagrelor groups. An increase in IMR ($\Delta\mathrm{IMR}_{\mathrm{post}} \geq 0$) was observed in 1 (12.5%) patient in Clopidogrel group, whereas it is observed for 4 (50%) patients in Ticagrelor group (p-value =

0.282).

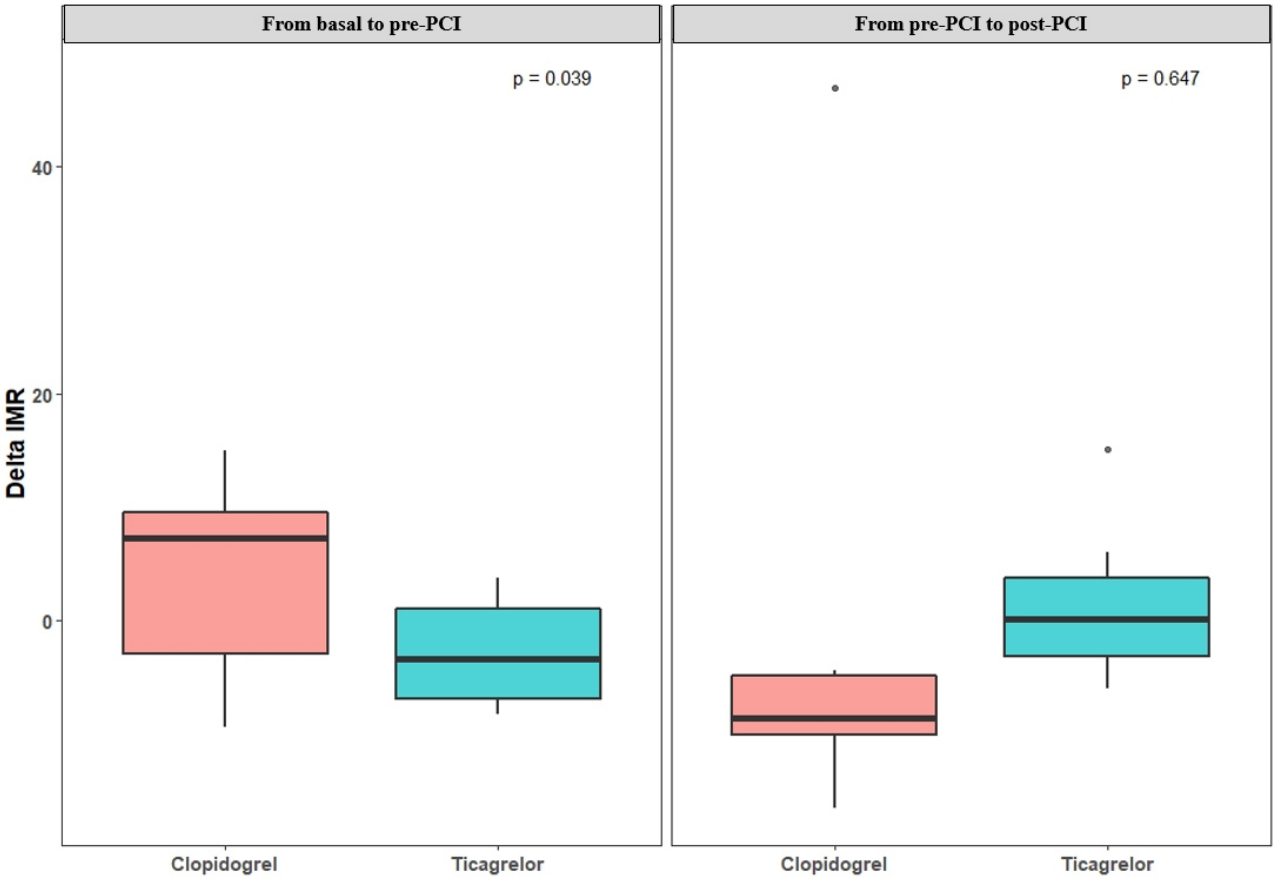

Figure 4: **Primary endpoints.** Difference in IMR from basal to pre-PCI (PRE) and from pre-PCI to post-PCI (POST), colored by treatment group.

C. High microcirculatory resistance (IMR >29) at baseline and before PCI.

At baseline, there were 2 patients with high microcirculatory resistance, all in Clopidogrel group. After treatment, and before PCI, all patients showed IMR≤29, except for one patient in Clopidogrel group.

2.3.3.3.5 Secondary endpoints

A. Myocardial necrosis associated with PCI damage, assessed by cardiac biomarkers.

PCI-related myocardial infarction is defined as post-procedural increase in Troponin more than 5 times the 99th percentile of the upper reference limit for patients with baseline negative

myocardial necrosis markers or an increase in CK-MB more than the 99th percentile of the upper reference limit.

Eleven patients showed MI post PCI, 6 of them from Clopidogrel group and 5 of Ticagrelor group, not revealing significant differences (p-value = 0.487).

B. Absolute resistance value after PCI.

There were no significant differences between IMR post PCI between groups as shown in **Table 3**.

2.3.3.3.6. Subgroup analysis: obesity

Four obese patients were assigned to each group. One of the obese patients, of Clopidogrel group, presented two diseased vessels. Only for the basal IMR measurement, a trend to higher values of IMR was observed for higher values of BMI ($r = 0.479$, p-value = 0.033). Nevertheless, ΔIMR were similar for obese patients than for non-obese patients.

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3. DISCUSSION

Since the publication of the articles collected in the present thesis, further researches and investigations on each topic has taken place thanks to the effort made worldwide by other research groups. In this section we provide a summary of these novel findings, allowing also to better understand the contribution made by our research to the advancement in knowledge.

- *Intracoronary physiology in three-vessel disease: Simplified hybrid algorithms for pressure wire interrogation exploiting advantages of a baseline and contrast Pd/Pa ratio indexes to predict stenosis significance (*Publication Number 1 in the thesis, par. 2.1.1.*)*

Maximal hyperaemia is the crucial prerequisite to assess FFR correctly. However, despite evidence and recommendations from guidelines, use of FFR is far from being frequent[1] and the need for administering adenosine is one of the reasons for this underutilization. Data from the DEFINE FLAIR and iFR Swedeheart trials[2,3] have demonstrated that a non-hyperemic resting indices like iFR-guided strategy constitutes an alternative to FFR interrogation, delivering consistent patient outcomes at one year of follow-up while significantly reducing patient discomfort, procedural time, and costs and allowing multiple vessels interrogation without need of adenosine administration saving time and costs. However, some physicians do not still have access to this technology mainly because it depends from the use of a dedicated guidewire and console. In these cases, other indexes like resting Pd/Pa ratio, universally available in any pressure wire console, could be an alternative to FFR also combined along with FFR in hybrid diagnostic flow-charts. For these aforementioned reasons, alternative ways to circumvent the need for adenosine were required to increased adoption of physiology, especially at the time when our trial was planned. For this reasons we designed the multicenter prospective SPARE trial (SimPlified Hybrid Algorithms for pressure wire interrogation exploiting advantages of a baseline and contrast Pd/Pa ration index to predict stenosis significance) included in the present thesis aiming:

i. to test and compare the accuracy of Pd/Pa and contrast medium injection (cFFR) to FFR;
ii. to test the agreement between an FFR-only strategy and both the previously proposed hybrid Pd/Pa-FFR[4] and cFFR-FFR[5] algorithms; and

iii. to test and compare the efficiency of three different multi-step hybrid algorithms (Pd/Pa-FFR; cFFR-FFR and a novel Pd/Pa-cFFR-FFR) in terms of agreement with an FFR only-strategy (cut-off value of ≤ 0.80) evaluating the proportion of patients free from adenosine and additional medium contrast administration.

We found that a simple algorithm to interrogate coronary stenosis with pressure guidewires, applicable to any available FFR system and consisting of sequential measurements of the translesional pressure ratio (at baseline, contrast-induced and during hyperemia), reduces dramatically the need of hyperemic agents for physiological interrogation whilst maintaining an high classification agreement with FFR as reference.

All previous findings were confirmed by the present study as a hybrid Pd/Pa-FFR strategy would be potentially able to avoid adenosine administration in 47% of patients, whereas a cFFR-FFR strategy in 86% of them maintaining an high classification agreement (>95% for both) with FFR. Moreover, we actually expand previous finding proposing to integrate these methodologies into a novel three steps strategy (Pd/Pa-cFFR-FFR) demonstrating that the use of adenosine might be unavoidable in a very small proportion of cases (10% of patients), thus leading to a reduction in adenosine-related drawbacks as well as to an accelerated functional assessment process making the physiologic evaluation of coronary stenosis simpler and more widespread than nowadays maintaining an high classification agreement. In a recent systematic review and meta-analysis[5] on adenosine-free indexes, cFFR showed an high correlation, predictivity and accuracy when FFR in used as reference (area under curve for accuracy of cFFR = 0.95; 95%CI 0.94–0.96) and it was significantly higher compared to Pd/Pa (0.86; 95%CI 0.80–0.93) confirming the potential advantage of our step-by-step algorithm to properly interrogate a stenisis with minimal use of contrast and adenosine.

This attitude is currently embraced by many researchers as, in the last years, several Resting non-hyperemic pressure ratios (NHPRs)[6] have been introduced with iFR being the first (and, currently, the only one) index validated[2,3] in clinical trials. Other NHPRs have become commercially available, such as the diastolic hyperemia-free ratio (Boston Scientific, Marlborough, Massachusetts), diastolic pressure ratio (Opsens Medical, Quebec, Quebec, Canada), and resting full-cycle ratio (Abbott, Abbott Park, Illinois). These NHPRs are also proprietary and can be used only with the software provided by the vendors. In comparison, our study proposed a hybrid flow-chart that is actually feasible with any software or console being

universally available the Pd/Pa ratio, the cFFR and FFR. In any case, the widespread of such hybrids multistep protocols or different NHPRs will finally result in wider adoption of physiology-guided PCI worldwide ultimately leading to a better patient care.

- *Intracoronary physiology and imaging in Left Main Coronary Artery disease (*Publication Number 2 in the thesis, par. 2.1.2.*).*

In this study was performed a systematic review on the safety of LMCA stenosis deferral based on IVUS or FFR. The main finding is that the safety of LMCA revascularization deferral based on IVUS or FFR seems to be associated with a similar risk of MACE at medium term being the per year of follow-up occurrence of overall MACE 5.1% (95% CI 1.9-8.2) in the FFR group and 6.4% (95% CI 3.1-9.7) in the IVUS group. Moreover, several different clinical and anatomical conditions related to each technique showed an interaction with outcome. This work represents to the best of our knowledge the first objective and quantitative comparison between the two available adjunctive invasive diagnostic tools recommended in clinical guidelines for ambiguous LMCA assessment.

Potential drawbacks related to FFR and IVUS use in LMCA were disclosed in our study. Among all predictors, for example, the use of lower doses of intracoronary adenosine (OR 1.39 [1.02 -1.89]; 95% CI, p = 0.041) resulted as independent predictors of MACE in FFR studies while plaque burden at the MLA site (OR 1.34, 95% CI 1.03 – 1.73; p=0.025) resulted as independent predictors of MACE in IVUS.

Regarding IVUS, although different MLA cut-offs were used across the studies, we observed that the rate of MACE was similar between studies that used a larger and smaller MLA cut-off: 6.2% and 5.6% for studies with MLA cut-off = 6 mm vs. 5.1% for MLA cut-off = 7.5 mm). Although a MLA of 6 mm^2 has been shown to be a valid cut-off for clinical decision making and has been used also in the EXCEL trial[7], it is reasonable that a lower cut-off value of even 4.5 mm^2 for the MLA may translate into acceptable similar long-term clinical outcomes especially in relation with ethnicity and body mass index[8]. A previous U.S. study[9] reported a cut-off value of 5.9 mm2 (sensitivity, 93%; specificity, 94%) for an FFR < 0.75. Conversely in LITRO study[10] 36% of the patients with an LMCA-MLA <6.0 mm^2 showed an FFR > 0.80 and they are at risk of undergoing unnecessary treatment. Finally, among the 54 LMCA lesions with MLA > 4.5 mm^2, 13 (24.1%) had an FFR of <0.80[11,12]

Integrating together imaging and physiology in LMCA assessment

On the ground of these data, in 2019, the expert consensus[13] document of the European Association of Percutaneous Cardiovascular Interventions has proposed a two-steps diagnostic flow chart in order to integrate the use of imaging (IVUS) and physiology during the assessment of an intermediate LMCA stenosis (**Figure 1**). Since in our study several different variables related to each technique showed an interaction on outcome, an approach combining both anatomical and functional information is most likely the safer approach be kept in mind when approaching the evaluation of an ambiguous LMCA.

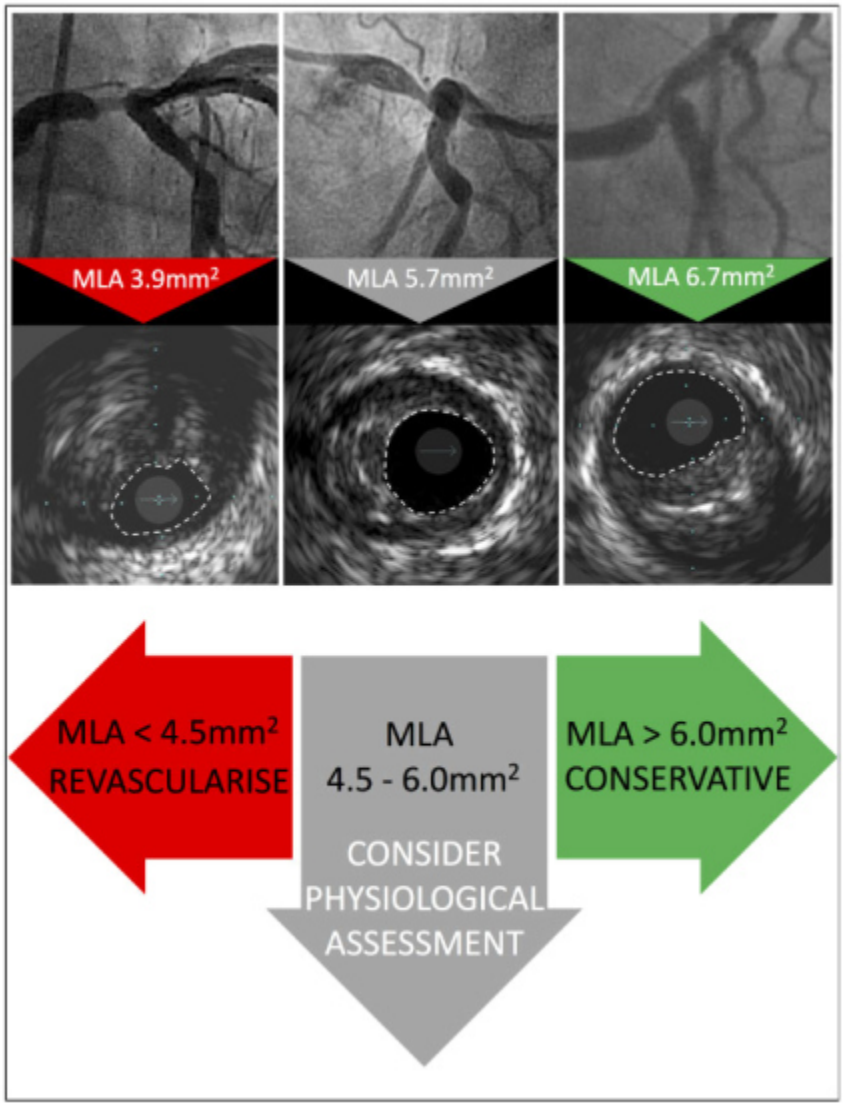

Figure 1. A schematic representation of the diagnostic flow-chart suggested in the expert consensus document. In cases of Minimal Lumen Area (MLA) between 4.5 and 6.0 mm^2, operator should be considered a physiology assessment to interrogate the stenosis.. Reproduction with permission from Johnson TW, et al. Eur Heart J 2019 Aug 14;40(31):2566-2584

Role of the iFR in LMCA assessment

The iFR could potentially simplify the functional assessment of stenosis severity in the LMCA mainly to avoid adenosine drawbacks in case of bifurcation stenoses, where multiple measurements are often performed in both daughter branches and a pullback recording should be

performed to confirm the localization of the LMCA stenosis and exclude the influence of others downstreams stenosis[14]

In a study[15] including 90 LMCA intermediate stenosis, iFR showed an excellent diagnostic performance to identify significant stenoses using the established FFR cutoff of 0.8 (AUC = 0.84; $p < 0.001$; sensitivity of 80% and a specificity of 78%.). The study demonstrated that the assessment of LMCA stenoses with iFR is a reliable adenosine-free alternative but was not powered to validate an iFR diagnostic cutoff for the LMCA and did not aim to evaluate the clinical outcome of an iFR-guided PCI strategy. Notably, the classification agreement between the iFR and the FFR was recorded in 81% of case. To this regard, the ongoing iLITRO study (ClinicalTrial.gov NCT03767621) will provide additional information on the diagnostic concordance between the iFR and the FFR in this setting

The only dedicated study to date is the DEFINE LM registry[16]. This multicenter observational study included patients in whom LMCA stenosis was deferred (51.9%) or revascularized (48.1%) according to an iFR cutoff of 0.89. At a median follow-up period of 30 months, the primary endpoint occurred in 15 patients (9.2%) in the deferred group and 22 patients (14.6%) in the revascularized group without differences (HR: 1.45; 95% CI: 0.75-2.81; $p = 0.26$), thus indicating that deferral of revascularization of LM stenosis on the basis of iFR appears to be safe. Future studies should validate this results and using randomized controlled designs or larger registry studies.

- *Safety of NCL deferral in ACS setting (*Publication Number 3 in the thesis, par. 2.1.3.*)*

In our study we compare the outcomes of FFR-guided revascularization or deferral of vascularization in patients with SAP and ACS NCL in a large database encompassing individual data from 8,579 patients from 3 registries and 2 RCT. In a total of 5129 patients (22.7% presenting with ACS and 77.3% presenting with SAP) revascularization was deferred. Deferral was significantly more common in the SAP group compared with the ACS group (61% vs. 55%; $p < 0.01$). The primary composite outcome (the 1-year incidence of MACE, a composite of death, nonfatal myocardial infarction, or unplanned revascularization procedures) occurred significantly more often in deferred patients with ACS compared with patients with SAP (4.46% vs. 2.83%; p

< 0.01). This finding remained statistically significant after adjusting for potential confounders (hazard ratio: 1.72; 95% CI: 1.17 - 2.53; p < 0.01) The difference in MACE was driven mainly by unplanned revascularization procedures (ACS 3.34% vs. SAP 2.04%; p = 0.02). In patients who underwent revascularization on the basis of FFR ≤0.80, MACE rates were numerically higher compared with those among deferred patients, with no difference in MACE at 1-year follow-up between the ACS and SAP groups (6.51% vs. 6.20%; adjusted HR: 1.21; 95% CI: 0.88 to 1.26; p = 0.24). The main findings of our study is that.

Along with the publication of our paper, an editorial by Claessen and Van Wijk was published in the same Journal in which they recognized the importance of the paper as well as they stressed some methodological issues of the work. Firstly, because of different definitions of clinical presentation in the participating studies, it was not possible to identify patients presenting with ACS-NSTEMI, ACS-STEMI, or unstable angina in the overall dataset, precluding subgroup analyses in these distinct types of ACS. This is relevant because differently from SAP setting, there are many potential causes that can lead to an increased risk of events in case of FFR interrogation during ACS and some of them could potentially be more or less marked according to the ACS type. For example, as reported by other authors, occasional misdiagnosis of the culprit stenosis could have occurred during the acute decision making process, especially in ACS-NSTEMI while is very uncommon in STEMI. This is relevant because previous research exploring the culprit vessel in the early post-STEMI phase showed dynamic changes in the infarcted myocardial bed associated with a non-quiescent microvascular hyperemic response and hyperemic flow secondary to thrombus embolization, coronary vasospasm, endothelial dysfunction, vascular stunning, intramyocardial hemorrhage etc. However, these phenomenona primarily described for ACS-STEMI was also reported for NSTEACS due to embolisation of active plaque material or thrombotic material. Consequently, we have to recognize this limitation due to the attempt of merge together the largest evidence available from different studies and we cannot provide any exploratory analyses in this setting precluding any conclusions regarding the need for greater attention in the course of different type of ACS. Additionally, if a patient needed unplanned revascularization during follow-up, it was not possible to ascertain whether this event was related and the collection of lesion location and subsequent percutaneous coronary intervention location during follow-up would have added valuable additional insights. Finally, the findings of our study refer to the use of FFR as a physiological index and cannot be applied to NHPRs used to assess

NCL in patients with ACS. Despite these limitations, Claessen and Van Wijk[17] recognized the value of our study being to date the largest individual patient database exploring the FFR performance in ACS. Consequently, someone might be wondering is the FFR is the best modality for the evaluation of NCL during ACS or if we have other alternatives.

As previously reported by other investigators[18,19], the accuracy of FFR in predicting outcomes among patients with ACS may not be equivalent to FFR when applied in SAP patients. Mechanistically, this can be explained by a failure to achieve maximal hyperemia during ACS (which is associated with a rise in zero flow pressure and left ventricular filling pressures, enhanced sympathetic drive and blunted coronary vasodilation) because of transient impairment of the microcirculation[20–25]. Notably, decreased CFR after an acute MI involves both culprit and NCL, owing to the combination of post-occlusive hyperemia, myocardial necrosis, hemorrhagic microvascular injury, compensatory hyperkinesis, and neurohumoral mechanisms.

On the matter of fact, in a recently published research[26] after successful primary PCI, NCL hemodynamic measurements were performed and repeated at 1-month follow-up. The total number of hemodynamically significant FFR (defined as ≤0.80) values was 11 (15.1%) at the acute moment vs 19 (26.0%) at 1-month follow-up (P = 0.06). Conversely, iFR remained constant as the total number of hemodynamically significant iFR value (≤0.89) was 17 (23.3%) at the acute moment vs 14 (19.2%) at 1-month follow-up (P = 0.58). Therefore, this study provides new evidence supporting the hypothesis that FFR measurements in the acute setting of ACS may lead to misclassification of the severity of NCL in up to 15% of cases, compared with subacute FFR measurements. On this topic, a combined analysis[27] of the DEFINE-FLAIR and iFR-SWEDEHEART trials showed that the 1-year MACE rate was numerically lower in deferred patients with ACS in the iFR arm compared with the FFR arm although without reaching a statistical significant value (n =12, 5.42% vs. n=14, 6.42%; p value NS).

In conclusion, our study provides useful insights into clinical outcomes after FFR-guided deferral of revascularization for patients with ACS but it should not limit the implementation of physiology in this important subset of patient in which presence of bystanders NCL is common and a proper classification of any residual intermediate stenosis could help physician in avoiding unnecessary PCI. Consequently, studies properly designed to confirm our findings and to assess differences among hyperemic or NHPRs in the setting of ACS should be object of future trials.

- *PRotective Effect on the coronary microcirculation of patients with DIabetes by Clopidogrel or Ticagrelor (PREDICT): study rationale and design. A randomized multicenter clinical trial using intracoronary multimodal physiology (*Publication Number 5 in the thesis and PREDICT trial results, par. 2.3.*)*

PREDICT is the first randomized trial to compare in patients with DMT2 the effect on the coronary microcirculation of Ticagrelor vs Clopidogrel. The study was conducted in patients with SIHD using multimodal physiology assessment, performed both before and after PCI with DES implantation. Although the trial was stopped prematurely due to slow patient enrolment, valuable insights on the effect of Ticagrelor on the coronary circulation of diabetic patients were obtained. The main findings could be summarized as follows:

1. In diabetic patients, the administration of Ticagrelor was associated to a significant decrease in microcirculatory resistance (delta-IMR) that was not observed in the Clopidogrel group.
2. As a result of this effect, as soon as 48 hours after initiation of treatment, IMR values were significantly lower in patients treated with Ticagrelor than with Clopidogrel.
3. Treatment with Ticagrelor was not associated to significant changes in microcirculatory resistance values over PCI, compared with Clopidogrel.

Several groups of investigators have found IMR to be an independent predictor of long-term survival in ACS patients undergoing PCI[28–30] and recently two RCT trials reported on this topic. Overall, the information obtained in these studies is in agreement with the results of the PREDICT trial. Furthermore, some of the original observations made in our study complement those made by other authors using different study designs. This is because PREDICT is the only study that has focused on patients with DMT" and that has measured the effect of treatment initiation of Clopidogrel and Ticagrelor on microcirculatory resistance.

The reducing Micro Vascular Dysfunction in Revascularized STEMI Patients by Off-target Properties of Ticagrelor (REDUCE-MVI)[31] randomized 110 patients with STEMI to receive a loading dose of Ticagrelor and a maintenance dose of Ticagrelor (n=56) or Prasugrel (n=54) after primary percutaneous coronary intervention (PPCI). The primary outcome was coronary

microvascular injury at 1 month, as determined with the IMR in the infarct-related artery. Cardiovascular magnetic resonance (CMR) imaging was performed during the acute phase and at 1 month and also plasma level of adenosine was tested in both groups.

Differently from PREDICT, microvascular function was assessed in the ACS setting, after a successful PPCI and after one month. Therefore, no data regarding the immediate effect of Ticagrelor vs. Clopidogrel on microcirculation before PCI are available for comparison. According to REDUCE-MVI primary outcome, IMR was not superior in Ticagrelor or Prasugrel-treated patients (21 [IQR 15–39] vs. 18 [IQR 11–29], respectively; p=0.08). This finding is similar to PREDICT, with no differences in IMR measured post-PCI in Ticagrelor or Clopidogrel group (15.67 ± 6.39 vs. 17.50 ± 14.39 respectively; p=0.725). We can hypothesize that downstream embolization of microthrombi or atheroma dislodged from the coronary stenosis as a result of its manipulation during PCI create a notable damage of microcirculatory status without significant differences related to P2Y12 of choice. Additionally, no significant differences in recovery of the microcirculatory status was reported within the first month. No difference in infarct size was observed at CMR imaging among two drugs as well the occurrence of microvascular obstruction was not different in patients on Ticagrelor or Prasugrel (28% vs. 41%; p=0.35). Plasma adenosine concentrations were not different during the index procedure and during maintenance therapy with Ticagrelor or Prasugrel. However as specified by authors, measurement of endogenous plasma concentration is very challenging because of the extremely short half-life of adenosine and rapid cellular uptake.

Another group recently reported results from the PLEIO trial[32] (Comparison of Ticagrelor and Clopidogrel on Microcirculation in Patients with Acute Coronary Syndrome). Following a PCI performed in a ACS culprit vessel, FFR, CFR and IMR were measured in the same artery at the end of PCI and repeated after 6 months of Clopidogrel or Ticagrelor therapy (1:1 randomization). As in REDUCE-MVI and PREDICT, no differences were found immediately after PCI, Interestingly, compared with Clopidogrel, 6-months treatment with Ticagrelor was associated with a more favorable changes in the microcirculation subtended to the ACS culprit vessel. IMR value was significantly lower in the Ticagrelor group than the Clopidogrel group (15.57±5.65 versus

21.15±8.39, p<0.01), and CFR was higher in the Ticagrelor group than in the Clopidogrel group (3.85±0.72 versus 3.37±0.76, p<0.01).

Conversely, few studies currently explore the role of Ticagrelor in producing microvascular modification in SIHD. Recently an RCT trial from Korea reported a cohort of 61 patients admitted for stable angina without non-significant coronary artery disease and randomized in a 1 : 1 : 1 ratio to receive drugs for at least 7 days: (i) Ticagrelor 180 mg loading and then 90 mg twice daily (n = 22), (ii) Ticagrelor 180 mg loading and then 45 mg twice daily (n = 19), or (iii) Clopidogrel 300 mg loading and then 75 mg once a day (n = 20). Multimodal coronary physiology (including FFR, CFR and IMR) was performed once at time of coronary angiography after excluding presence of significant CAD. The study included also 30% of patients with T2DM. There was no difference in the FFR between both the groups. CFR was not significantly different in both the groups (2.0 [IQR, 0.7 - 5.5] vs.1.85 [IQR, 1.13 - 3.60], p = 0.731) while IMR was significantly lower in patient group receiving Ticagrelor than Clopidogrel group (15.0 [IQR, 12.00 - 21.00] vs. 47.5 [IQR, 20.75 - 67.50], p = 0.014). This result is in line with PREDICT even if a part of the population received a lower dose of Ticagrelor and IMR was widely distributed with higher level in Clopidogrel vs Ticagrelor group. Unfortunately, this trial does not include a follow-up assessment of the same parameters precluding any speculation on microcirculatory changing over a longer period of Ticagrelor treatment. On the matter of fact, while in PREDICT we could not detect any protective benefit of Ticagrelor therapy in periprocedural changes of microcirculatory resistance, compared with Clopidogrel, it remains plausible that the lower microcirculatory resistances documented following instauration of Ticagrelor treatment might have a salutary effect in patients with SIHD chronically treated with this antiplatelet agent.

Interesting data on this topic will be surely provided in the next future from the ongoing TAPER-S trial[33] (Ticagrelor and preconditioning in patients with stable coronary artery disease) This is a prospective, open-label, pilot study that enrolled patients with stable multivessel CAD requiring staged FFR-guided PCI. Participants will be randomized in 1:1 ratio either to Ticagrelor or to Clopidogrel from 3 to 1 days before the scheduled PCI. The primary endpoint is the delta (difference) between ST segment elevations (in millimeters) as assessed by intracoronary electrocardiogram (ECG) during the two-step sequential coronary balloon inflation in the target vessel. Secondary endpoints included changes in CFR, IMR and FFR at the end of PCI. This study

started in 2018 with the aim of enroll 60 patients for evaluate the primary endpoint and the estimated study completion is expected within 2020[34].

Summarizing available data, we can draw some hypothesis regarding potential microcirculatory status produced by Ticagrelor administration in comparison to other P2Y12 without the property of blocking the equilibrative nucleoside transporter-1 receptor:

a. The effect in terms of lowering the microcirculatory resistance seems to start early after drug administration in patients presenting with SIHD while no differences observed in terms of CFR improvement;
b. Immediately after PCI and within the first month, no differences were recorded comparing Ticagrelor-treated patients vs. Clopidogrel or Prasugrel treatment in both ACS and SIHD
c. Compared with Clopidogrel, 6 months of Ticagrelor therapy significantly improved microvascular dysfunction (lower IMR and higher CFR) in patients initially admitted for an ACS and treated with PCI and stents

<u>From physiology to clinical outcome</u>

The favorable effect of Ticagrelor on microcirculation may explain the improved clinical outcome seen in clinical trial. Recently the THEMIS RCT trial[35] enrolled more than 19,000 patients 50 years of age or older with SIHD and T2DM without a history of myocardial infarction or stroke randomized to receive either Ticagrelor plus aspirin or placebo plus aspirin. Patients included are at high risk of CV events, defined as previous history of PCI or CABG or angiographic evidence of >50% stenosis of at least 1 coronary artery

The study reported a lower incidence of ischemic cardiovascular events in Ticagrelor plus aspirin group (7.7% vs. 8.5%; HR = 0.90; 95% CI 0.81-0.99; p = 0.04), whereas the incidence of major bleeding was higher (2.2% vs. 1.0%; HR 2.32; 95% CI 1.82-2.94; p<0.001) as was the incidence of intracranial hemorrhage (0.7% vs. 0.5%; HR 1.71; 95% CI, 1.18-2.48; p = 0.005). For this reason, for patients with T2DM and known coronary disease who fit the THEMIS enrollment criteria, the addition of Ticagrelor to aspirin is to date not recommended[36]. However in a

prespecified analysis of THEMIS (THEMIS-PCI[37]) patients with SIHD and T2DM who have a history of previous PCI showed a significant benefit from adding Ticagrelor on top of aspirin.

Given the favorable effect on microcirculation network of Ticagrelor, future studies should be done in SIHD to test the efficacy of a single APT strategy with Ticagrelor at standard or low dose in reducing ischemic events without the risk of increase bleedings. This should be particular relevant in T2DM patients or in other subgroups of patients like obese with an abnormal coronary microcirculation.[38]

Limitations

Even fully recognizing the limitation of our result obtained without reaching the planned sample size, all investigators agreed in reporting the current analysis considering several important reasons. First of all, as mentioned in the discussion, while some studies were published in ACS setting, very few data are available regarding physiological consequence of administering Ticagrelor in a T2DM patients presenting with SIHD. Having the privilege of collecting and analyzing such data and having observed a significant difference in one of the primary endpoints even without collecting the planned sample size, we judged our result worthy of being reported. Secondly, others studies performed in ACS setting suffered the same difficulties in recruiting patients with a large part of them excluded due to the inherent complexity of any study designed to perform multiple invasive interrogation of microcirculation[31]. Finally, we hope that our findings may help in properly design future studies exploring microcirculatory temporal changing in SIHD.

4. CONCLUSIONES

Las conclusiones de la tesis, a partir de los trabajos de investigación realizados con fisiología coronaria en escenarios clínicos y angiográficos complejos e incluyendo los resultados del ensayo clínico randomizado PREDICT son las siguientes:

- Durante los últimos años ha aumentado de forma significativa la evidencia científica respaldando la fisiología intracoronaria para la toma de decisiones clínicas en el contexto del tratamiento de la enfermedad coronaria;
- No obstante, existen distintos escenarios clínicos en los que no hay suficiente evidencia científica o el papel de la fisiologia está menos establecido;
- En el contexto de la enfermedad multivaso de las arterias coronarias, o en otras situaciones en las que se requieran múltiples mediciones fisiológicas intracoronarias o deba evitarse la administración de adenosina, pueden considerarse estrategias alternativas al FFR para la valoración funcional de las estenosis coronarias. Hemos demostrado que el uso de algoritmos híbridos que combinan la relación de presiones translesionales (Pd / Pa) obtenida en reposo, tras la inyección de medio de contraste (cFFR) y, finalmente, durante hiperemia, permiten alcanzar un rendimiento diagnóstico similar al del FFR, disminuyendo de forma dramática el uso de adenosina y/o contraste como agentes hiperémicos;
- Diferir la revascularización coronaria en el contexto de una estenosis moderada del tronco común izquierdo basado en mediciones realizadas con FFR o con ultrasonido intravascular (IVUS) se asocia a medio plazo, con un riesgo de eventos aceptable y similar en un seguimiento a medio plazo, aunque se ha demostrado que son diferentes las características clínicas y anatómicas específicas que pueden comprometer la fiabilidad de cada técnica;
- La enfermedad coronaria multivaso es común en pacientes con síndrome coronario agudo (SCA). Diferir la revascularización de estenosis en arterias no culpables de un SCA en base a mediciones de FFR se asopcia a una mayor incidencia de eventos cardiovasculares mayores (MACE) cuando se compara con diferir la revascularización en el contexto de la angina estable en base al FFR. La revascularización no planificada dentro de los primeros meses es el factor que contribuye de forma más significativa al mayor número de eventos cardiovasculares documentado en los pacientes con SCA y enfermedad multivaso;
- Los índices fisiológicos basados en el cociente de presiones coronarias permiten evaluar la severidad de las estenosis epicárdicas, pero no proporcionan información sobre el estado de la microcirculación. A diferencia de los grandes vasos de

capacitancia del epicardio, la microcirculación tiene un papel dinámico en el flujo sanguíneo coronario, basado en la regulación constante de su resistencia a través de varios mecanismos que incluyen componentes metabólicos, miogénicos, endoteliales y neurales. Desde el punto de vista clínico, el conocimiento completo de todos los índices fisiológicos para identificar y cuantificar la presencia de disfunción microcirculatoria es fundamental para poder obtener información pronóstica;

- El estudio PREDICT (PRotective Effect on the coronary microcirculation of patients with DIabetes by Clopidogrel or Ticagrelor) es el primer ensayo aleatorizado que compara el efecto sobre la microcirculación coronaria del fármaco antiplaquetario Ticagrelor frente al fármaco Clopidogrel en el contexto de la cardiopatía estable en el paciente con diabetes mellitus antes y después de revascularización coronaria con uso de stents. Los resultados del estudio muestran que en pacientes diabéticos, la administración de Ticagrelor se asoció a una disminución significativa de la resistencia microcirculatoria (evaluado por el índice IMR) que no se observó en el grupo de Clopidogrel. Como resultado de este efecto, tan pronto como 48 horas después del inicio del tratamiento, los valores de IMR fueron significativamente más bajos en los pacientes tratados con Ticagrelor que con Clopidogrel. Por el contrario, el tratamiento con Ticagrelor no se asoció a cambios significativos en los valores de resistencia microcirculatoria durante la angioplastia coronaria, en comparación con Clopidogrel. Sin embargo, la validez de estos resultados requiere estudios adicionales con tamaños poblacionales grandes.

4. CONCLUSIONS

The conclusions of the thesis, based on the research work carried out with coronary physiology in complex clinical and angiographic settings and including the results of the PREDICT randomized clinical trial, are the following:

- In the recent years, a growing body of evidence supports the use of intracoronary physiology for clinical decision-making in the context of the treatment of coronary disease.
- Nevertheless, there are still a paucity of data regarding the safety of revascularization deferral on the ground of intracoronary physiology in specific anatomical and clinical complex subset of patients in which the role of physiology is less established.
- In the context of MVD, or in other situations where multiple intracoronary physiologic measurements are required or administration of adenosine should be avoided, alternative strategies to FFR may be considered for the functional assessment of coronary stenosis. We have shown that the use of hybrid algorithms that combine the translesional pressure ratio (Pd / Pa) obtained at rest, after injection of contrast medium (cFFR) and, finally, during hyperemia, allow to achieve a diagnostic performance similar to FFR, dramatically reducing the use of adenosine and / or contrast as hyperemic agents;
- Deferring coronary revascularization in the context of intermediate LMCA stenosis based either on FFR or IVUS is associated with an acceptable and similar risk of events at mid-term follow-up. Notably, several different clinical and anatomical conditions related to each technique showed an interaction with outcome.
- MVD is common in patients with ACS. Deferring revascularization of a non-culprit stenosis using FFR in the setting of ACS is associated with a higher incidence of major cardiovascular events (MACE) when compared to deferring revascularization in the setting of stable angina based on FFR. Unplanned revascularization within the first few months is the factor that contributes most significantly to the highest number of documented cardiovascular events in patients with ACS and MVD.
- Physiological indices based on coronary pressure make it possible to assess the severity of epicardial stenosis, but do not provide information on the state of microcirculation. Unlike the great capacitance vessels of the epicardium, microcirculation has a dynamic role in coronary blood flow, based on the constant regulation of its resistance through various mechanisms including metabolic, myogenic, endothelial, and neural components. From the clinical point of view, the complete knowledge of all the

physiological indices to identify and quantify the presence of microcirculatory dysfunction is essential to be able to obtain prognostic information.

- The PREDICT trial (PRotective Effect on the coronary microcirculation of patient with DIabetes by Clopidogrel or Ticagrelor) is the first randomized trial to compare the effect on coronary microcirculation of the antiplatelet drug Ticagrelor versus the drug Clopidogrel in the context of stable heart disease in patients with diabetes mellitus before and after coronary revascularization with stents. The results of the study show that in diabetic patients, the administration of Ticagrelor was associated to a significant decrease in microcirculatory resistance (delta-IMR) that was not observed in the Clopidogrel group. As a result of this effect, as soon as 48 hours after initiation of treatment, IMR values were significantly lower in patients treated with Ticagrelor than those treated with Clopidogrel. In contrast, Ticagrelor treatment was not associated with significant changes in microcirculatory resistance values during coronary angioplasty, compared to Clopidogrel. The validity of these results requires further studies with large population sizes.

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PART III

Appendix

List of publications

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Other scientific achievements

Oral presentations (related to the present thesis)

1. PRotective Effect on the coronary microcirculation of patients with DIabetes by Clopidogrel or Ticagrelor (PREDICT) CVMD Research Summit, Rome, 2017

2. Revascularization Deferral of Nonculprit Stenoses on the Basis of Fractional Flow Reserve 1-Year Outcomes of 8,579 Patients. Transcatheter Cardiovascular Therapeutics, San Diego, 2018

3. Fractional Flow Reserve in Acute Coronary Syndrome Setting. Cardiovascular Research Technology, Washington, 2018

4. Safety of Revascularization Deferral Based on Physiological Significance. Cardiovascular Research Technology, Washington, 2020

Courses

1. Cardiovascular Research Technology 2018-2020 - Invited faculty

2. Transcatheter Cardiovascular Therapeutics, 2016 - Invited faculty

3. GISE Congress 2015-2020 - Invited faculty

4. Intracoronary Guidance in Complex PCI. Madrid, April 2019 - Invited faculty

5. Beyond Angiography: sharing evidence and experience on contemporary coronary diagnostics, Madrid, February 2014 - Invited faculty

6. Beyond Angiography: sharing evidence and experience on contemporary coronary diagnostics, Madrid, June 2015 - Invited faculty

Awards

1. Awarded to 2015 International Fellowship Grant - Cardiovascular Research Technology meeeting, Washington, USA

2. Awarded to 2016 Scholarship – C3 meeting – Orlando, USA

3. Awarded to 2016 and 2017 Young Leadership Grant - CRT meeeting, Washingto, USA

4. Awarded to 2017 SCAI FALL Fellows Course – Las Vegas, USA

Research Grants

1. PREDICT RCT (PRotective Effect on the Coronary Microcirculation of Patients With DIabetes by Clopidogrel or Ticagrelor; clinical trial number NCT02698618; PMID 28526024)"-
   Industry Grant. Role: Co-PI

2. PULSE RCT. Angiographic control vs. ischemia-driven management of Patients undergoing percutaneous revascularization of the Unprotected Left main coronary artery with Second-generation drug Eluting stents: the PULSE trial; clinical trial number NCT04144881
   Young Researcher (under 40 years), Public Grant. Role: Co-PI

Others scientific activities

Webcreator, designer, master of www.cardiogroup.org, an electronic platform for case report forms (eCRF) to gather data in clinical trials.

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